EXHIBIT 1

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation	**Docket No.: 22-md-3043 (DLC)**
This Document Relates to: All Actions	

RULE 26(a)(2) EXPERT DISCLOSURE OF WENDY K. CHUNG, M.D., Ph.D.

Pursuant to Federal Rule of Civil Procedure 26(a)(2), defendants disclose Wendy K. Chung, M.D., Ph.D. as an expert witness in this case.

I. SUMMARY OF OPINIONS AND BASES

The opinions Dr. Chung intends to offer in this case and the bases and reasons for them are contained in her report in this case, attached as Exhibit 1. A list of materials Dr. Chung has reviewed and/or considered in forming these opinions, in addition to those cited in her report, is attached as Exhibit 2.

II. QUALIFICATIONS AND PUBLICATIONS IN PREVIOUS TEN YEARS

A copy of Dr. Chung's *curriculum vitae*, which identifies her publications over the previous ten years, is attached as Exhibit 3.

III. COMPENSATION

Dr. Chung's hourly rate is $600.

IV. EXPERT TESTIMONY IN PRECEDING FOUR YEARS

In the last four years, Dr. Chung has testified as an expert witness as follows:

- *Gharbi v. USA*, Case No. 19-cv-1943 (M.D. Pa)
- *Santiago-Hudson v. CHCA*, Texas (Case No. unknown)
- *Melton v. Miner*, Case No. 19-cvs-3127 (N.C. Sup. Ct., Cumberland Co.)
- *Daniels-Feasel v. Forest Pharmaceuticals, Inc.*, Case No. 1:17-cv-4188 (S.D.N.Y.)

Dated: July 21, 2023

Respectfully submitted,

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IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation **This Document Relates to: All Actions**	**Docket No.: 22-md-3043 (DLC)**

EXPERT REPORT OF WENDY K. CHUNG, M.D., Ph.D.

EXPERT REPORT OF WENDY K. CHUNG, M.D., Ph.D.

I.

INTRODUCTION AND SUMMARY OF OPINIONS

1. I am a clinical and molecular geneticist certified by the American Board of Medical Genetics. I am Chief of the Department of Pediatrics at Boston Children's Hospital and the Mary Ellen Avery Professor at Harvard Medical School. For more than two decades, I have studied and clinically cared for patients with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Over the course of my career, I have identified over 50 new genes linked to human diseases, three of which are named after me. Using advanced sequencing methods, I have identified and studied dozens of new genes and variants that cause ASD.

2. This report identifies the robust and rigorously replicated scientific evidence in the published literature demonstrating the known genetic etiologies of ASD and ADHD. My report also addresses the published epidemiological studies on prenatal acetaminophen (APAP) exposure and outcomes purportedly relating to ASD and/or ADHD to assess whether these studies have properly accounted for genetic confounders. Finally, my report addresses the various methodologies and data used by plaintiffs' experts in their expert reports.

3. For the reasons described in this report, I have arrived at the following opinions:

i. ASD is a neurodevelopmental condition marked by persistent deficits in social communication and interaction, and restricted, repetitive patterns of behaviors, interests, or activities. ADHD is a different neurodevelopmental disorder with a distinct etiology and diagnosis. ADHD is defined as a persistent pattern of inattention and/or hyperactivity-impulsivity.

ii. Genetic variants account for most known causes of ASD and ADHD. These genetic variants include both inherited mutations that are transmitted from generation to generation and spontaneous *de novo* (new) mutations that arose sporadically in an individual organism and were not inherited from its parents. Hundreds of genes and genetic mutations have been linked to ASD and ADHD, and this number continues to grow each year through advancements in genetic research, gene discovery, and clinical genetic testing.

iii. Genetic mutations and genetic variants that cause ASD and ADHD are highly heritable, with heritability estimates for both conditions being on average 80-90%.

iv. ASD and ADHD have genetic overlap with other conditions, such as cerebral palsy, epilepsy, and psychiatric disorders. Having parents or first-degree relatives with one of these genetically overlapping conditions increases the risk of ASD or ADHD in the child.

v. There is no reliable scientific evidence that acetaminophen changes expression in the human brain, either through epigenetics or other mechanisms, of genes relevant to the etiology of ASD or ADHD. There are also no data or study suggesting that some sort of genetic susceptibility to acetaminophen detoxification causes ASD or ADHD among individuals prenatally exposed to acetaminophen.

vi. Pregnant acetaminophen users, and their families, tend to have a higher genetic/ familial risk of giving birth to a child with ASD and/or ADHD. This background risk is demonstrated across different types of studies, including those utilizing sibling-controls, polygenic risk scores (the integration of many common variants in many genes into a single score to predict disease risk), negative controls, and disease-free

controls, as well as studies that report the distribution of characteristics of pregnant acetaminophen users compared to pregnant non-users.

vii. Adequately controlling for genetic and familial confounding in observational studies through statistical adjustment can be difficult for a variety of reasons including the following:

a. Genetic/ familial confounding cannot be controlled by adjusting for one or several proxies of genetic/ familial confounding because multiple potential factors may independently confound the results. For example, controlling or adjusting for a single proxy of genetic risk, such as maternal psychiatric disorder, will not adjust for other maternal genetic contributions or any paternal genetic contribution.

b. Even if a study simultaneously adjusts for multiple proxy factors, incomplete or imperfect information about what these factors are will likely result in residual confounding.

c. There are no reliable proxy factors to adequately adjust for *de novo* genetic mutations.

d. Measurements of common genetic liability, such as polygenic risk scores, are currently incomplete and imperfect, and only capture a subset of common inherited variants but do not evaluate rare inherited mutations or *de novo* mutations. Additionally, they only capture common variants that are presently known.

viii. Many of the observational epidemiological studies on acetaminophen and the potential increased risk of ASD or ADHD examine behaviors or symptoms that are not reliable

surrogates for these neurodevelopmental conditions. ASD and ADHD are well-defined neurodevelopmental disorders based on very specific diagnostic criteria. Accordingly, to be scientifically reliable, any method used for reaching a causal inference on whether a proposed risk factor can cause ASD and/or ADHD must examine studies that report on clinically diagnosed ASD and ADHD.

ix. The epidemiological studies that are posited to show an association between prenatal acetaminophen exposure and the development of ASD or ADHD do not establish that acetaminophen, as opposed to background genetic and/or familial factors, was responsible for the observed associations. This is true for both ASD and ADHD:

a. **ASD:** None of the small number of studies evaluating whether *in utero* acetaminophen exposure increases the risk of ASD adequately controlled for genetic/familial confounding.

b. **ADHD:** Almost all studies evaluating whether *in utero* acetaminophen exposure increased the risk of ADHD did not adequately control for genetic/familial confounding. The only study that employed a sibling-controlled design and looked at clinically diagnosed ADHD reported no association. Moreover, a more than 2-fold increased risk of ADHD with long-term acetaminophen use effectively disappeared in the sibling-controlled analysis. The authors estimated the effect of this familial/genetic confounding to confer a 177% increased risk of ADHD on any child whose mother used acetaminophen long term in a prior pregnancy (irrespective of whether the child was actually exposed to acetaminophen). Thus, any observed associations

between *in utero* exposure to acetaminophen and ADHD are likely the result of genetic/familial confounding.

x. Given the lack of a valid association between prenatal acetaminophen exposure and ASD or ADHD, any causal inference is inappropriate and scientifically unreliable.

II.

QUALIFICATIONS

4. In 1990, I received a B.A. in biochemistry and economics from Cornell University. I obtained a Ph.D. in genetics from the Rockefeller University in 1996 and a medical degree from Cornell University Medical College in 1998. Between 1999 and 2000, I performed a residency in pediatrics at Columbia Presbyterian Medical Center. From 2000 to 2002, I was a Fellow in Clinical Genetics at the Division of Clinical Genetics, Department of Pediatrics, at Columbia. From 2002 to 2003, I was a Fellow in Molecular Genetics, also at Columbia Presbyterian.

5. During my tenure at the Department of Pediatrics at Columbia University, I served as the Chief of the Division of Clinical Genetics, and as the Director of the Diagnosis Initiative Seeking Care and Opportunities with Vision for Exploration and Research (DISCOVER) program. In these roles, I studied and directed clinical care of patients with ASD, often co-presenting with ADHD, together with other rare and complex conditions.

6. For over two decades, my research has focused on the genetic underpinnings of ASD, ADHD, and other neurodevelopmental disorders. As the Principal Investigator of Simons Searchlight, I have studied genetic neurodevelopmental disorders in thousands of individuals around the world. I have led National Institutes of Health (NIH) funded

research programs across a wide range of conditions, including neurodevelopmental disorders and birth defects. I am the Principal Investigator of the Simons Foundation Powering Autism Research for Knowledge (SPARK), which is currently the largest ASD cohort in the world with over 375,000 study participants. I am Principal Investigator of an NIH funded Autism Center of Excellence grant studying early neurodevelopment and behavior of individuals at genetic risk of ASD.

7. I have authored or co-authored more than 700 peer-reviewed papers in journals, including *Nature*, *Science*, *The New England Journal of Medicine*, the *Journal of the American Medical Association*, *Nature Genetics*, and the *American Journal of Human Genetics*, among others. I have also published more than 80 chapters in medical textbooks.

8. When I was the Kennedy Family Professor of Pediatrics (in Medicine) and Medical Director of the Genetic Counseling Graduate Program at Columbia University, I taught courses on genetics and neurodevelopmental disorders to medical and other graduate students. I have also lectured on ASD across the United States. In 2014, I gave a TED talk with over 4.5 million views entitled "Autism: What We Know (and What We Don't Yet Know)."

9. I am a member of the Board of Directors of the American Society of Human Genetics, the National Academy of Medicine, and the American Association of Physicians. I was also a member of the Council for the National Human Genome Research Institute at NIH.

10. I have received the New York Academy Medal for Distinguished Contributions in Biomedical Science, American Academy of Pediatrics (AAP) Young Investigator Award, and the Medical Achievement Award from Bonei Olam, a non-profit organization founded to help people suffering from infertility and risk of hereditary disorders in future children, among other honors. I was a member of the Glenda Garvey Teaching Academy at Columbia University

and have won many awards for teaching, including the Charles W. Bohmfalk Award for Distinguished Contributions to Teaching, American Medical Women's Association Mentor Award, and Columbia University Presidential Award for Outstanding Teaching.

11. A complete description of education, training, and professional experience is set forth in my *curriculum vitae*.

III.

GENETICS IN HUMAN DISEASE

12. Genetics is the study of genes and heredity, i.e., how certain characteristics (called phenotypes) that result from individual variations in genetic instructions are passed from parents to children.

13. Genetic instructions direct the development and function of organisms and are stored as a sequence of four different nucleotides (bases) of deoxyribonucleic acid (DNA). These bases are adenine [A], thymine [T], cytosine [C], and guanine [G]. In animals and plants, DNA is packed into chromosomes with the help of proteins called histones. Humans typically have 23 pairs of chromosomes.

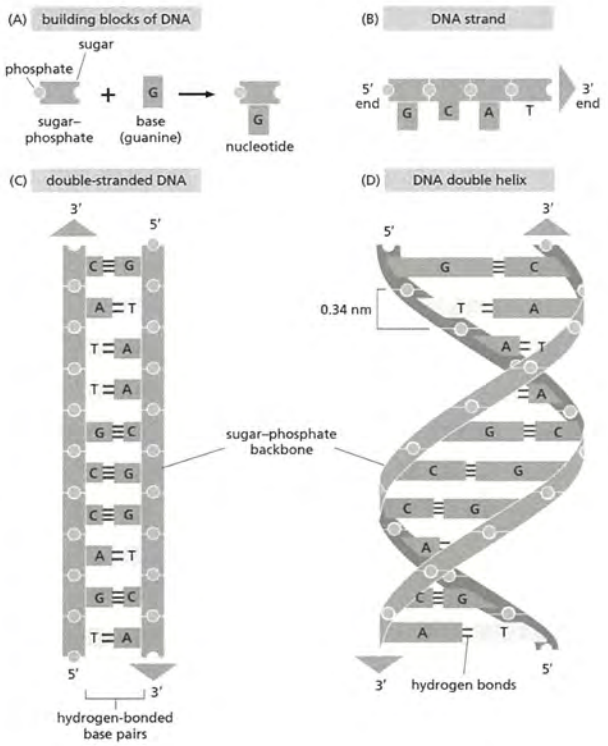

Fig. 1. Graphic depiction of DNA. Reproduced from Figure 4-3 of Molecular Biology of the Cell (7th Edition).

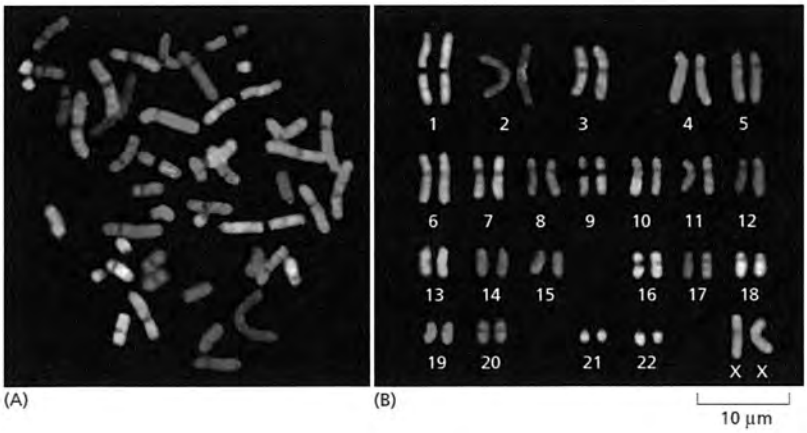

Fig. 2. The complete set of human chromosomes. Reproduced from Figure 4-11 of Molecular Biology of the Cell (7th Edition).

14. The genome is the complete set of DNA of an organism. A gene is a section of DNA that encodes a protein and thus has a specific function within a cell. The human genome contains approximately 3 billion base pairs and is estimated to have approximately 20,000 genes.

15. A gene is "expressed" when the information encoded in the gene is used in synthesizing a gene product, such as protein, which ultimately conveys a particular function inside a cell. Within a single gene are protein coding regions ("exons") and, in most genes, non-protein coding regions ("introns" and regulatory regions). Exons are transcribed into messenger ribonucleic acid (mRNA). Transcriptional regulation requires relevant proteins (known as transcription factors) to be bound to non-coding regulatory regions of the genome, such as promoters and enhancers. mRNA is transported from the nucleus to the cytosol and then translated into proteins. All the exons in an organism are collectively called the "exome."

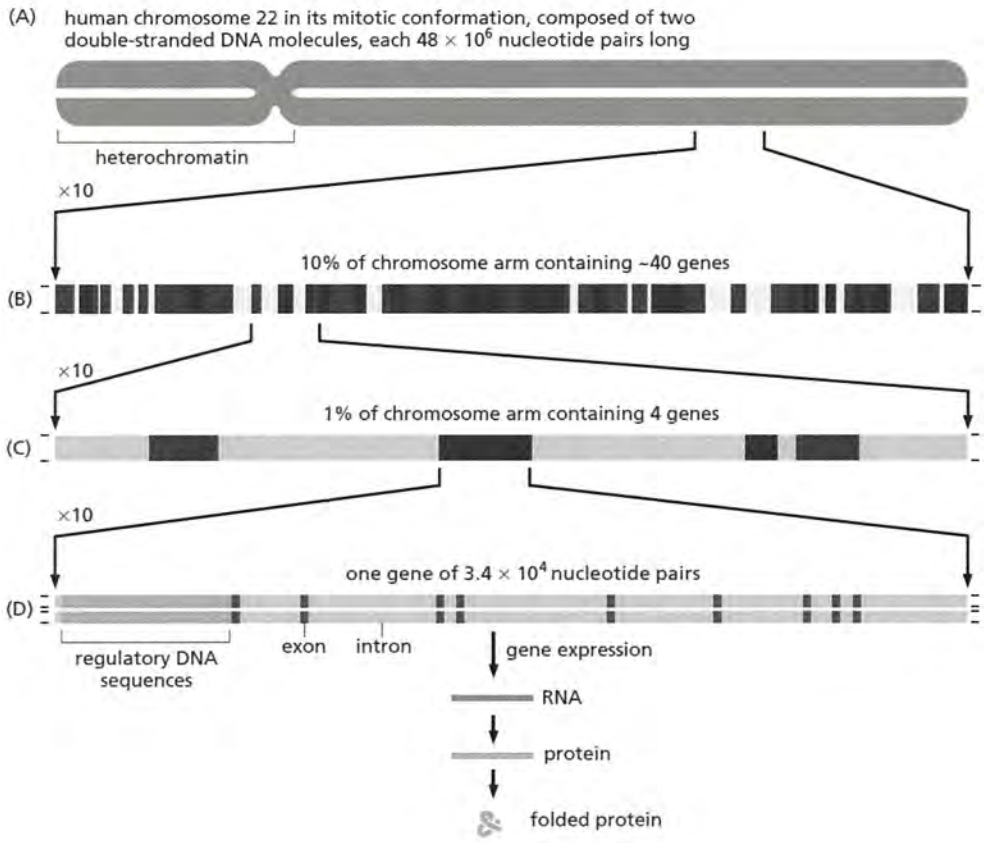

Fig. 3. The organization of genes and non-coding region. Reproduced from Figure 4-14 of Molecular Biology of the Cell (7th Edition).

16. Only 2% of the entire human genome is comprised of coding sequence or exons. The rest of the genome is comprised of "non-coding" regions that do not encode proteins. Certain parts of these non-coding regions regulate gene expression (Scacheri 2015). However, these non-coding regions have not yet fully been characterized.

A. Variation in DNA Sequence

17. Humans share approximately 99.9% of their genome in common with each other, but small differences in DNA sequences make each person unique. These differences in DNA sequence can change protein production in terms of where (which organ in the body and cell

type), when (timing), and how much (levels) of the protein is made. These differences are responsible for individual appearances (e.g., eye color, hair color) and also affect the propensity to develop diseases or disorders, such as cancer.

18. Chromosomal abnormalities can cause variation in DNA sequence, usually in the amount of DNA in a chromosome. A chromosomal abnormality is a disorder characterized by a numerical (i.e., increase or decrease) or a structural alteration of a single or multiple chromosomes. A well-known example is Down Syndrome, when an individual has a complete or partial extra copy of chromosome 21.

19. There are other types of variations in DNA sequences. Some genetic variants do not have a phenotypic effect and are benign, while other genetic variants can cause a disease or disorder.

B. Causes of Mutations

20. Mutations can occur either by errors in DNA replication or by DNA damage. Causes of DNA damage include radiation, chemicals, and infectious agents, such as viruses. All eukaryotic cells (i.e., cells that possess a clearly defined nucleus) have evolved multiple mechanisms that are carefully coordinated to correct the errors in DNA replication, as well as the potentially deleterious effects of DNA damage. For example, when a cell senses issues in DNA replication or DNA damage, the cell stops its cell cycle progression and repairs the problem. Failure to properly correct the DNA leads to genetic mutations. For example, several autosomal recessive DNA repair defects make patients very sensitive to UV radiation from the sun and likely to develop skin cancers.

C. Genetic Mutations

1. Inherited Mutations

21. Inherited genetic mutations are passed down from a parent to the offspring through the egg or sperm (Acuna-Hidalgo 2016). These genetic mutations and their resultant variants are transmitted through the germline and are detectable in all tissues of the child and their parents (Mohiuddin 2022).

22. There are two types of inherited variants: common and rare. Common variants have a frequency of greater than 1% in the population. The gene variant for blood type O is a common variant. Rare variants have a frequency of less than 1% (Schork 2009). For example, the genetic variant causing Huntington Disease (a progressive brain disorder) is rare.

2. De Novo Mutations

23. Mutations that are not passed down from a parent but are new in the offspring are known as "*de novo* mutations" (Acuna-Hidalgo 2016, Mohiuddin 2022). *De novo* mutations and their resultant variants can be identified by comparing the genetic sequence of the offspring to that of both parents. There are on average 100-200 *de novo* mutations in every person.

24. There are two types of *de novo* mutations (Acuna-Hidalgo 2016). Some *de novo* mutations occur in the gamete (sperm or egg) prior to fertilization. Studies have reported an increase in the number of *de novo* mutations in the gamete with advancing parental age (e.g. Goldman 2016). Jónsson et al. 2017 found that the rate of the *de novo* mutations in fathers' sperms increased 4 times more quickly with advancing age than the rate of *de novo* mutations in mothers' eggs. Post-zygotic mutations are *de novo* mutations that occur after fertilization. Certain post-zygotic mutations occur very early in embryonic development (Acuna-Hidalgo 2016). Mutations that occur during embryonic development cause an individual to have two or more genetically different sets of cells (mosaicism) and are called mosaic mutations (Freed 2014, Acuna-Hidalgo

2016, Lim 2017). Some researchers have estimated that the frequency of the early embryonic mosaic mutations is approximately 3 to 7% (Ju 2017).

3. Single Nucleotide Variants / Polymorphisms

25. A single nucleotide variant (SNV) is a DNA sequence variation that affects only a single nucleotide (adenine, thymine, cytosine, or guanine) in the genome sequence (Trudsø 2020). If a single nucleotide in the genome sequence is relatively common and altered in greater than 1% of the population, it is referred to as a single nucleotide polymorphism (SNP).

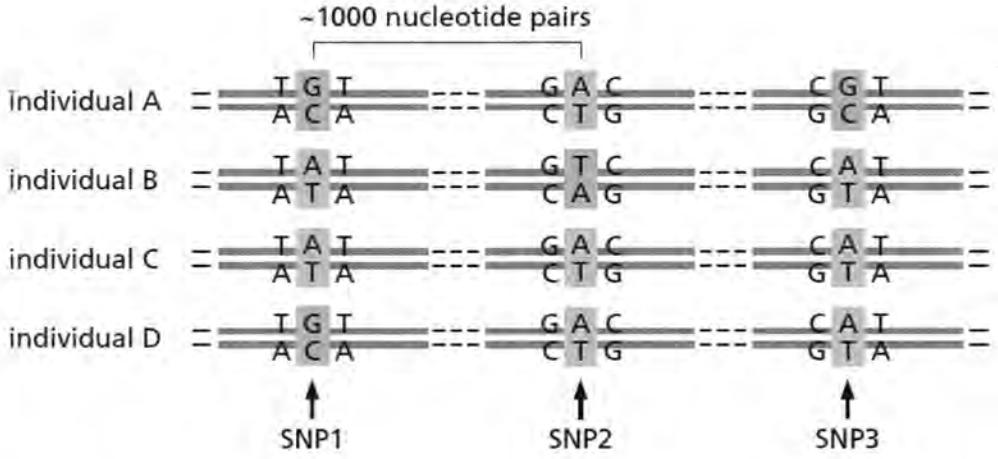

Fig. 4. SNP. Reproduced from Figure 8-52 of Molecular Biology of the Cell (7th Edition).

26. Advances in DNA sequencing technologies have allowed for whole exome sequencing ("WES"), as well as whole genome sequencing ("WGS"), resulting in identification of SNPs. SNPs are typically used for a Genome Wide Association Study ("GWAS"), which identifies genetic variants associated with a specific disease or disorder. Using aggregation of many SNPs, a polygenic risk score (PRS) can be calculated to estimate the genetic risk or susceptibility of an individual for a disease or disorder, such as ASD and ADHD, by mathematically combining the probabilities of multiple SNPs together to generate a risk score using many SNPs (Aguilar-Lacasaña 2022, Grimm 2020).

4. Insertions and Deletions

27. Mutations can also occur in multiple consecutive nucleotides. For example, insertions and deletions (also known as indels) affect a small length of DNA, usually one to 50 base pairs, that has either been inserted into or deleted from the genome. Larger structural variations generally involve at least 50 nucleotides (Mahmoud 2019). For example, a copy number variant (CNV) is a duplicated or deleted DNA segment of greater than 50 base pairs in length that changes the number of copies of a specific DNA segment within the genome. Several CNVs have been identified to be associated with a range of neurodevelopmental disorders, including intellectual disabilities, ASD, ADHD, and schizophrenia.

28. For purposes of this report, I use the term "genetic mutation" to broadly encompass many types of DNA genetic variations that cause single gene (monogenic) disorders or contribute to etiology of multiple gene (polygenic) disorders.

D. Genetic Testing

29. Several tests can be performed to determine if an individual has genetic variants responsible for a particular condition. WGS has been a first-tier diagnostic test since 2021 (Manickam 2021). Other less comprehensive tests include WES and chromosomal microarray, which looks for extra or missing chromosomal segments. These tests utilize DNA of the individual as well as his or her parents to interpret the significance of any variants that might be causing the individual's condition. These test results would be interpreted by a board-certified Medical Geneticist who is experienced in clinical genetics and genomics.

E. Gene Expression

30. Gene expression is tightly regulated by complex mechanisms to allow for specificity across diverse tissues and cell types and over time to allow the body to develop and

function correctly. Gene expression regulation occurs at two levels: at the level of transcription, which alters the amount of mRNA to be produced from a particular gene, and at the post-transcription level that regulates the translation of mRNA into proteins.

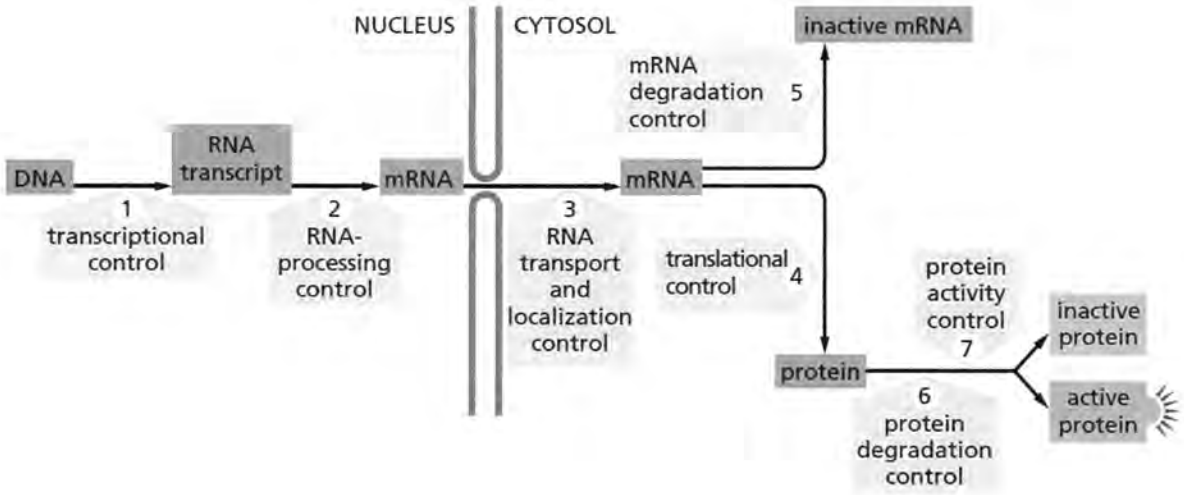

Fig. 5. Gene expression regulation. Reproduced from Figure 7-6 of Molecular Biology of the Cell (7th Edition).

31. Regulation at the transcription level is controlled by three elements: (1) transcription factors, (2) regulatory regions, and (3) epigenetics.

1. Transcription factors

32. Because relevant transcription factors need to bind to the corresponding regulatory regions in the genome to initiate or stop transcription, levels and functions of such factors influence transcription. Further, because transcription factors need to be in the nucleus in order to bind to the corresponding regulatory region in the genome, intracellular localization of the transcription factors also affect the level of transcription.

33. Mechanisms to control the level, function, and intracellular localization of transcription factors are complex. For example, in order for a specific transcription factor to be localized to the nucleus, the protein needs to be transported from the cytosol by a protein called a nuclear transporter. If expression of the relevant nuclear transporter decreases, the amount of the transcription factor inside the nucleus decreases and the transcription of a specific gene can be lowered.

34. Within a cell, multiple proteins work together in a series of interactions to achieve a specific function. These interactions are called biological pathways. Biological pathways can have local or distant effects. For example, some biological pathways have effects that are limited to the specific cell (e.g., controlling cell replication). Other biological pathways cause cells to produce substances, such as hormones, that travel through the bloodstream to target distant cells.

35. Biological pathways can be influenced by chemical cues, triggered by events, such as infection, stress, or nutritional status.

2. Regulatory Regions

36. Sequence variations in regulatory regions of the genome can affect transcription. Regulatory regions are part of the non-coding genome where transcription factors bind to regulate transcription. Mutations in a regulatory region can make it difficult for a transcription factor to bind and thus can affect the level of transcription of the gene.

3. Epigenetics

37. Epigenetics is a field of study investigating whether and how a person's behaviors and environment can affect the expression of gene(s) through chemical modifications to

the DNA. The prefix "epi" means "over" and epigenetics indicates features that are "on top of" the DNA sequence.

38. Epigenetic changes include methylation of DNA and modification of histone that bind to DNA and open up the chromosome to make certain regions more accessible to binding of transcription factors that regulate gene expression. Unlike genetic changes to the DNA sequence, epigenetic changes are dynamic. For example, epigenetic changes due to aging were reported to be modifiable by changing diet and lifestyle intervention (Fitzgerald 2021).

39. Epigenetic changes are not consistent across the entire human body (Jambhekar 2019). Assessing epigenetic modifications in one tissue is not a surrogate for the epigenetic modifications in another tissue.

40. Regulation in transcription through these three mechanisms occurs everywhere in the body throughout human and animal development. Humans, as well as other multiple cell organisms, develop from a single fertilized egg into a body consisting of multiple different organs, such as the eyes, the brain and the liver, all of which have complex developmental processes and different functions. For example, the proteins expressed by the brain and the liver are different.

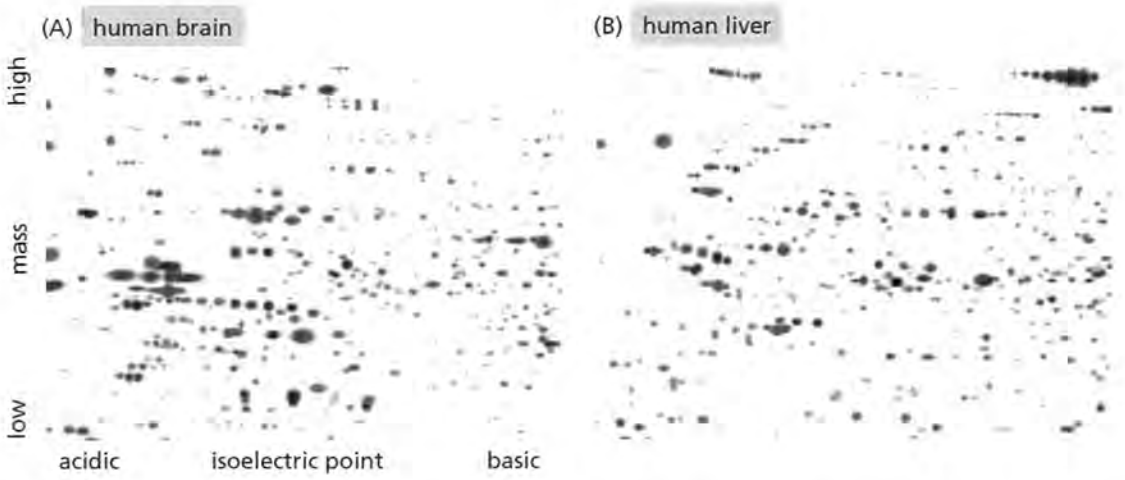

Fig. 6. Differences in the protein expression patterns by the brain and the liver. Reproduced from Figure 7-4 of Molecular Biology of the Cell (7th Edition).

41. Thus, when analyzing gene expression changes, it is important to analyze the expression (a) at the relevant location and (b) at the relevant time period. It is also important to consider environmental conditions that must be controlled. Because of the complex nature of gene expression and the multitude of factors that influence the expression of genes, it is often difficult to identify the precise trigger of changes in gene expression.

F. Genetics and Genomics

42. While the field of genetics focuses on the study of individual genes, genomics focuses on the study of the entire genome. Genomics became a distinctive scientific discipline with the completion of sequencing of the human genome. Genomics provides the opportunity for rigorous, unbiased analyses because all genetic factors can be equally assessed. Unlike many other scientific fields, preconceived notions or hypotheses are not required. Instead, genomicists follow the data in an unbiased manner and arrive at the scientific truth. Although not always recognized, many scientists in other fields intentionally or unintentionally design and conduct experiments and interpret their data in a way that supports their preconceived hypotheses.

43. The field of genomics is built on principles of open data sharing that allow for the aggregation of large genomic data sets that are freely available to the scientific community. Having the same data sets available to all scientists allows for rigor and reproducibility of analyses and enables iterative improvements of analytical methods as scientists build upon the work of others. Because scientists are all analyzing the same data, there is a scientific ecosystem of checks and balances whereby results and their interpretations are not overstated. The genomic data sets that are currently analyzed frequently include in excess of 50,000 cases and 100,000 controls for many conditions, including autism. Such large sample sizes provide opportunities to divide the cohorts into discovery and replication cohorts to ensure rigor and reproducibility of findings. These massive sample sizes frequently identify genes for disease with p values smaller than a 1 in trillion chance that the result could be by chance alone. By comparison, other fields of science accept p values of .05 as statistically significant, even though the result has a 1 in 20 chance of occurring by chance alone. Thus, genomic studies and genomic analysis produce results that are highly reliable and have repeatedly stood the test of time.

G. Genetics Research for Disease Etiology

44. Heritability is the fraction of the variability of the phenotype that is due to inherited genetic factors. Heritability can be estimated using twin studies. Two types of twins are studied for this purpose: monozygotic twins (MZ), who are siblings from one fertilized egg, and dizygotic twins (DZ), who are siblings from two different fertilized eggs. Heritability is calculated by comparing the concordance rate – the probability that two people with shared genetic information will develop the same condition – of MZ twins with that of DZ twins. It is expressed using this formula:

$$h^2 = \frac{\text{Variance in DZ pairs} - \text{Variance in MZ pairs}}{\text{Variance in DZ pairs}}$$

45. Heritability does not account for all the genetic variants. For example, mosaic mutations (i.e., mutations that occur after a zygote is created) in one of the identical twins could make the twins discordant (i.e., decrease heritability), although the mutation explains the etiology of the condition for that twin. Therefore, the heritability calculation can underestimate the genetic contribution to the condition.

46. Modern genetic research goes beyond estimating heritability and focuses, in part, on understanding the genetic architecture of human diseases or disorders by identifying responsible genetic variants. The driving forces for modern genetic research are: (i) advancement of DNA sequencing technologies, such as WES and WGS; and (ii) technologies, such as GWAS, to analyze the potential association between genetic variants and a phenotype. WES focuses on sequencing all the exons, while WGS determines the sequence of all the nucleotides in the genome. These sequencing technologies, together with the analytical technologies (e.g., GWAS), have emerged in the last 15 years and have changed the landscape of modern genetic research.

47. PRS enables researchers to identify whether genetics may mediate potential associations. For instance, imagine a scenario where an epidemiological study finds an association between eating a high fat diet and an increased risk of depression. One can then study whether a high fat diet is also associated with the PRS for depression. If the PRS is also associated with the high fat diet, it would suggest that the observed association is driven by genetics, not the high fat diet itself.

48. PRS are, however, limited in several ways. First, PRS only capture genetic risk attributable to common inherited variants. In other words, PRS do not consider rare inherited mutations or *de novo* mutations. Second, the genetic variants used to calculate PRS have rapidly evolved over the last several years as the genetics community discovers additional common

variants associated with certain diseases. Thus, PRS even a few years old may not reflect current understanding. Given these limitations, GWAS are helpful to demonstrate that a genetic link exists but cannot be used to disprove a genetic link.

49. Modern genetic research has multiple complexities. First, for a disease or disorder that involves multiple genetic variants (such as polygenic disorders), the effect of each genetic variant is typically very small, and it requires a large sample size to provide adequate power to identify genetic variants with small effects. Second, there is still a technical limitation in DNA sequencing that makes it difficult to accurately read certain sections of the genome. Third, the ability to associate rare genetic variants of individually modest effect size with certain diseases or disorders is still developing. Fourth, available genetic testing can be limited if only a subset of genes is assessed.

50. For diseases or disorders that have a genetic etiology, as discussed, understanding the genetic architecture is critical for epidemiological studies assessing non-genetic risks because genetics would be a major confounding factor in the analysis.

IV.

GENETICS OF AUTISM SPECTRUM DISORDERS

A. ASD Background

51. ASD is a neurodevelopmental condition marked by persistent deficits in social communication and interaction, and restricted, repetitive patterns of behaviors, interests, or activities. A diagnosis of ASD requires a clinical diagnosis based on established criteria. There are no diagnostic laboratory tests for ASD, such as a blood test or imaging of the brain. To be diagnosed with ASD, an individual must have symptoms in three areas of persistent social communication and interaction: (1) deficits in social emotional reciprocity (e.g., trouble with back-

and-forth conversation), (2) deficits in nonverbal communication (e.g., abnormal eye-contact and body language), and (3) deficits in developing and maintaining relationships (e.g., lack of interest in others). In addition, a child must have at least two of four types of restricted, repetitive behaviors, including but not limited to: repetitive motor movements (lining up toys or flipping objects), echolalia (e.g., repeating words or phrases), rigid adherence to routines (e.g., eating the same food because of color or texture), fixated interests that are abnormal in intensity or focus (e.g., playing a certain game) or sensory issues (e.g., strong dislike to certain sounds or an adverse response to sounds or textures) (DSM-V 2013).

52. The definition of "autism" and associated diagnostic criteria, have changed over time. From 1994 to early 2013, the fourth edition of Diagnostic and Statistical Manual of Mental Disorders ("DSM-IV") recognized multiple subtypes of autism such as "autistic disorder," "Asperger's disorder," "childhood disintegrative disorder," "Rett's disorder," and "pervasive developmental disorder-not otherwise specified (PDD-NOS)" (DSM-IV 1994). In May 2013, the fifth edition ("DSM-V") superseded DSM-IV and combined the multiple ASD subtypes into a single definition of "autism spectrum disorder" (DSM-V 2013). The new definition of ASD, which merges together a spectrum of disorders, can make it difficult to compare results of studies of autism over time.

53. Because ASD is a spectrum of disorders that affects individuals in different ways, significant heterogeneity exists across individuals with ASD both in terms of types and severity of symptoms. For instance, individuals with "severe" or "profound" ASD may be non-verbal and/or diagnosed with other co-occurring conditions such as intellectual disability. By contrast, there are individuals on the autism spectrum, such as those who would have been previously diagnosed with Asperger's Syndrome, who are often described as gifted savants and

may be extremely talented in one or more areas even though they find social interactions challenging.

54. ASD is a common neurodevelopmental disorder with an estimated prevalence of 2.8% in US children aged 8 years (1 in 36 US children) (Maenner 2023). ASD prevalence has changed over time, in part due to changes in definitions and diagnostic criteria along with increased reporting, public awareness (Hansen 2015). For example, in 1990, legislation was passed to make autism an educational disability with efforts to identify and support children with ASD in schools (Pennington 2014). Over time, support for ASD research, services, and awareness has grown (Autism Cares Act 2019, Autism Act 2006). With increased awareness, more parents, pediatricians, and educators have learned how to recognize ASD symptoms and in turn more individuals have been diagnosed with ASD (Harris 2023). Another factor that accounts for the increased prevalence of ASD is the broadening of the definition of ASD per the DSM-V (Zeidan 2022). Multiple studies have shown that the overall incidence of ASD is relatively similar across populations (Wallace 2012).

B. ASD Genetics

55. Studies have established that genetic factors are the predominant cause of ASD. Twin studies have reported a heritability range of, on average, 80-90% for ASD (Tick 2016, Taylor 2020). Monozygotic ("identical") twins who share the same DNA sequence (except for *de novo* mutations) have a 77-88% concordance rate, which means if one identical twin has ASD, there is a 77-88% chance that the other twin will also have ASD. Importantly, the lack of 100% concordance between monozygotic twins does not necessarily support a role for non-genetic factors in the etiology of ASD. In addition to the effect of *de novo* (mosaic) mutations, discordance could be explained by the failure or lack of diagnosis of the "unaffected" twin. Among dizygotic

twins, who share only approximately 50% of their genetic information, there is a 31% concordance rate.

56. Family studies also support the genetic etiology of ASD. The relative risk for ASD in first-degree relatives (siblings or parent/child) is eight times higher than in the general population. Parental consanguinity (e.g., parents who share a common relative) or shared common ancestry is also associated with an increased offspring risk of ASD, likely due to the shared genetic variants among parents that combine in the offspring to increase the risk of ASD (Mamidala 2015).

57. There is no single gene responsible for the whole etiology of ASD. Instead, the genetic architecture of ASD is complex and many genes and genetic variants cause ASD.

58. Certain chromosomal abnormalities are known to cause ASD. For example, trisomy 21 (Down syndrome) is known to be associated with ASD in individuals with Down syndrome. A deletion or duplication of a chromosomal section account for ASD (2015 Sanders). For example, 16p11.2 deletion, which usually arises *de novo*, is reported to account for ASD in more than 1% of individuals with ASD (Levy 2011).

Table 1. Regions with Multiple dnCNVs in the SSC (FDR ≤ 0.1)

Band	Location (hg19)	dnCNVs (del/dup)	RefSeq Genes	Genes[a]	p Value (Corrected)	q Value (FDR)
1q21.1	chr1:146,467,203-147,858,208	5 (0/5)	13	–	0.00008	0.00002
3q29	chr3:195,747,398-197,346,971	3 (3/0)	21	–	0.14	0.05
7q11.23	chr7:72,773,570-74,144,177	4 (0/4)	22	–	0.004	0.001
7q11.23	chr7:73,978,801-74,144,177[b]	5 (0/5)	2	*GTF2I*, *GTF2IRD1*	0.00008	0.00002
7q11.23	chr7:74,455,447-74,488,775	3 (1/2)	1	*WBSCR16*	0.31	0.06
15q11.2-13.1	chr15:23,683,783-28,471,141	5 (0/5)	13	–	0.00008	0.00002
15q12	chr15:26,971,834-27,548,820[c]	6 (0/6)	3	*GABRB3*, *GABRA5*, *GABRG3*	1×10^{-6}	6×10^{-7}
15q13.2-13.3	chr15:31,245,880-32,515,849	4 (2/2)	7	–	0.01	0.002
16p11.2	chr16:29,655,864-30,195,048	13 (8/5)	27	–	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$
16q23.3	chr16:82,660,399-83,830,215[d]	3 (3/0)	1	*CDH13*	0.13	0.05
22q11.21	chr22:18,886,915-21,052,014	4 (2/2)	36	–	0.31	0.06

[a]Where ≤3 genes are present, they are listed to clarify the genomic location.
[b]This is the region of intersection between an atypical dnCNV and the Williams-Beuren Syndrome locus (see Figure S5).
[c]This is the region of intersection between an atypical dnCNV and the 15q11.2-13.1 locus (see Figure 6F).
[d]Three de novo deletions overlap at least one exon of this gene.

Table 1. Chromosomal abnormalities and ASD. Reproduced from Table 1 of Sanders 2015.

59. Certain monogenic disorders, for example, Fragile X, Rett syndrome, and tuberous sclerosis, are also known to cause ASD. Each of these single gene disorders accounts for less than 1% of ASD cases.

60. There are monogenic variants that are highly penetrant and by themselves can cause ASD. These variants can either be *de novo* or inherited. Individuals at the severe end of the autism spectrum, often with intellectual disability, are more likely to have *de novo* genetic mutations since these individuals usually do not reproduce to pass down these genetic variants to children. These *de novo* mutations generally affect genes critical for brain development and function and represent genetic causes of ASD beyond those accounted for in studies of heritability of ASD (Jamain 2003, Lord 2020). The relative risk of rare *de novo* variants is often 100-fold over the baseline risk of the population.

61. There are also inherited monogenic variants although less is known about this class of genetic variants. The currently known ASD monogenic variants are rare (i.e., less than 1% of the population). Research has currently identified at least 250 variants, and this number continues to rise. For example, in Satterstrom 2020, the authors performed whole exome sequencing of 35,584 persons, including 11,986 with ASD, and reported 102 ASD genes for which rare variants are associated with ASD. Just recently, two studies were published analyzing large ASD populations, and they continued to identify additional genes associated with rare variants and ASD (Fu 2022, Zhou 2022). The relative risk of rare inherited variants is often ~10 fold.

62. Individual common variants do not individually cause ASD but in combination polygenic variants together can cause ASD. Common variants are common (typically greater than 1% of the population carries the variant) and are of small, if any, effect on how the

body functions and therefore are transmitted to the next generation. In other words, there is little if any selective pressure against them. Each common variant contributes to the chance of ASD by a small and varying degree. There are likely to be at least 200 genes with common variants that confer a risk of ASD. An individual variant might be associated with a relative risk of ~1.1 or 1.2 or less. Any one person with ASD might have 50 or more risk variants that when combined increase the likelihood of developing ASD by 3-10 fold.

63. In aggregate, the contribution of common variants is estimated to account for approximately 50% of the risk of ASD (Klei 2021, Gaugler 2014). Rare inherited variants contribute approximately 35% of the risk of ASD. *De novo* mutations contribute the remaining 15%, approximately.

64. Research of common variants has not discovered all the responsible variants because it requires a large number of samples to identify them. The most recent GWAS using WGS analyzed 18,381 persons with ASD and 27,967 non-ASD controls and identified five genome-wide-significant common variants (Grove 2019). There are many more common genetic variants for ASD yet to be identified. For other traits such as height, thousands of contributory common variants have been identified.

65. The identification of responsible ASD genetic variants has shed light on the neurobiological origins of ASD. The functions of genes identified to date relate to synaptic function and neurotransmission, which control communication from one neuron to another, as well as functions that affect aspects of brain development, such as transcription, chromatin modification and cell migration. For example, a mutation in the gene encoding synaptic scaffolding protein SHANK3 was identified to be associated with ASD (De Rubeis 2014).

66. The etiology of ASD is also known to overlap with other neuropsychiatric disorders. For example, researchers focusing on a single copy number variant causing ASD, 16p11.2, found that individuals with the deletion had a higher frequency of multiple neuropsychiatric and neurodevelopmental disorders, such as ADHD, ASD, intellectual disability, as well as speech and developmental delay. (Hanson 2015, Steinman 2016). Overlap in genetic etiologies between cerebral palsy and ASD is also reported (2018 van Eyk).

67. Even with the increased sample sizes, there are limitations in sequencing and analysis technologies. For example, mosaic mutations that are not present in the whole body often require analysis of the body part where the mutations exist, and often that part of the body (e.g. the brain) is impossible to access in living individuals. Certain repetitive DNA sequences are difficult to sequence accurately. Further, researchers still have not uncovered the role of all the introns, regulatory, and other non-coding regions. The current estimate of the genetic contribution to ASD represents a floor or lower bound, and as we discover additional genetic variants to account for ASD, the proportion of the disorder attributable to genetic causes will certainly increase.

68. Environmental exposures that have been reported to be associated with ASD include thalidomide, misoprostol, valproic acid, maternal infections (i.e., rubella, cytomegalovirus), fever and/or maternal inflammation during pregnancy, neonatal hypoxia, and prematurity (Johnson 2010, Christensen 2013, Xu 2023). Studies, including genetic studies, are on-going to investigate these associations and potential confounding by genetics.

V.

GENETICS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

A. ADHD Background

69. ADHD is a neurodevelopmental disorder defined as a persistent pattern of inattention and/or hyperactivity-impulsivity. The DSM-V requires that several ADHD symptoms are present for at least 6 months before the age of 12, are documented as inconsistent with developmental level, and negatively impact directly social and academic/occupational activities in more than one setting (e.g., home, school, work). Additionally, the DSM-V states that certain lab findings that children with ADHD display as a group (e.g., magnetic resonance imaging) are not diagnostic (DSM-V 2013). Currently there is no biological marker (e.g., blood test or brain imaging) that is diagnostic for ADHD. Even in cases where testing demonstrates that individuals have genetic mutations known to cause ADHD, the DSM-V states that the ADHD presentation should still be clinically diagnosed (DSM-V 2013).

70. ADHD symptoms include inattention and/or hyperactivity-impulsivity. Inattention may present as wandering off task, lacking persistence, having difficulty sustaining focus, and being disorganized, but should not be due to defiance or lack of comprehension. For example, inattention and disorganization could be described as an inability to listen or frequently losing materials, at levels that are inconsistent with age or developmental level (DSM-V 2013). Hyperactivity refers to excessively inappropriate motor activity or fidgeting, tapping, or talkativeness. Impulsivity could appear as hasty actions that occur in the moment, a desire for immediate rewards, or an inability to delay gratification. Impulsive behaviors in children with ADHD may also be observed as social intrusiveness, including interrupting others excessively.

71. ADHD is the most common neurodevelopmental disorder in children. The Centers for Disease Control and Prevention (CDC) report that the prevalence of physician-diagnosed ADHD in US children aged 4 to 17 years old is 10.8% (Diallo 2022). Prevalence has also changed over time in part due to changing definitions and diagnostic criteria and increased awareness and screening (Visser 2014). For example, the DSM-IV (1994) required that ADHD functional impairments be "clinically significant;" by comparison, the DSM-V (2013) states that functional impairments must "reduce the quality of social, academic or occupational functioning." Additionally, the DSM-IV required that some hyperactive-impulsive or inattentive symptoms be present in the child before the age of 7, but the DSM-V (2013) increased the age range to include children who exhibit hyperactive-impulsive or inattentive symptoms before the age of 12 (Epstein 2013).

B. ADHD Genetics

72. Research has established that genetics are the predominant cause of ADHD (Faraone 2021). The heritability of ADHD is estimated to be an average range of 80-90% (Grimm 2020, Larsson 2014, Mattheisen 2022). Sibling and adoption studies have demonstrated that inherited genetic factors are the primary cause of ADHD in children. For instance, a study of ADHD patients and their siblings aged 5–17 years old found a 9-fold increased risk of ADHD in siblings of individuals with ADHD compared to siblings of controls (i.e., a child whose sibling did not have ADHD) (Chen 2008). In addition, adoption studies suggest that the observed increased risk of ADHD among family members is attributable to genetics, rather than shared environmental factors. In other words, if someone has a sibling with ADHD, that person is also at an increased risk of ADHD if the sibling is *biologically* related; however, an increased risk of ADHD was not reported in those with an *adopted* sibling with ADHD (Sprich 2000).

73. ADHD can be caused by common inherited variants, rare inherited mutations, and *de novo* mutations affecting one or more genes. These genetic contributions can be monogenic or polygenic. For example, an exome sequencing study of ADHD patients without a family history of ADHD reported cases with *de novo* missense mutations in brain-expressed genes (Kim 2017).

74. Recently, an international collaboration studied more than 200,000 individuals including 38,691 individuals with ADHD and revealed 27 risk loci for ADHD (Demontis 2023), strongly supporting the genetic etiology of ADHD. Because many of the variants implicated in ADHD are in genes that are expressed in the brain rather than other parts of the body, the authors concluded that the genomic data provided evidence that ADHD disrupts neurocognitive abilities.

75. Genetic research on ADHD is still ongoing, and there are limitations in research technologies, analytical methods, and genetic testing. As new ADHD genetic variants are discovered and the research advances, the genetic factors contributing to the etiology of ADHD are expected to increase.

76. Major risk factors for ADHD primarily relate to genetic and familial aspects. For example, the most consistently reported risk factors for ADHD include having a relative with ADHD, genetic variants (Faraone 2019), or parent-related risk factors including maternal gestational diabetes (Chen 2021), parental depression and bipolar disorder (Propper 2021), and parental smoking (Han 2015).

VI.

METHODOLOGICAL CONSIDERATIONS FOR EPIDEMIOLOGICAL STUDY DESIGNS

77. There are important methodological considerations for controlling genetic/familial confounding in epidemiological study designs. For instance, a **sibling-controlled analysis** can be useful for controlling genetic/familial confounding in observational epidemiological studies. A sibling-controlled design compares siblings born of the same mother (and ideally the same father) who are discordantly exposed, meaning one sibling was exposed and the other was unexposed to the exposure of interest. This allows investigators to partially control for inherited genetic factors by comparing the risk of disease among siblings, who share more DNA than unrelated individuals.

78. There are many examples of exposures that were initially thought to be ASD and/or ADHD risk factors until the implementation of sibling-controlled designs showed that the associations were actually driven by genetic/familial confounding. For example:

- A meta-analysis of prenatal antidepressant exposure and offspring ASD showed significant increased risks in population-based studies (n=7 studies); however, these associations attenuated to the null in a meta-analysis of sibling-controlled studies (n=4 studies) (Vega 2020). Notably, the associations were not fully attenuated to the null in analyses using psychiatric controls that account for maternal psychiatric diagnosis.
- A cohort study reported that labor inducing medication increased the risk of ASD in offspring, but the results were completely attenuated within the sibling analysis group (Oberg 2016). Another study reported labor induction was associated with statistically significant increased risks of offspring ADHD and low academic achievement.

Notably, the associations were substantially attenuated but remained significant in a cousin-controlled analysis. The associations were fully attenuated and were no longer significant in a sibling-controlled analysis (Wiggs 2017).

- A study of 13,411 sibling pairs reported that children delivered by cesarean section (C-section) were more likely to be diagnosed with ASD; however, the association did not persist (and attenuated to the null) in the sibling-control model (Curran 2015).
- Multiple studies reported that maternal smoking during pregnancy increased the risk of ADHD in children; however, the associations became attenuated and were no longer significant in sibling-controlled analyses (Obel 2016, Gustavson 2017, Huang 2018). This is because genetic factors directly influence the parental behavior that determine the "environmental exposure" and some of those same genetic factors are associated with the risk of ADHD. Once familial factor is controlled, the association with the environmental exposure (i.e., smoking) and the outcome (i.e., ADHD) is no longer demonstrable.

79. These examples broadly illustrate the importance of sibling-controlled designs to address genetic/familial confounding in studies of ASD and ADHD. Two additional examples—focusing on populations of women with prenatal infections who are likely to use acetaminophen—are discussed in more detail below.

80. The **Ginsberg et al 2019** Swedish population-based cohort study used a family-based design to evaluate whether prenatal infections were associated with ADHD in children. Prenatal infections were ascertained based on ICD-9 and 10 codes.[1] Outcomes were

[1] The International Classification of Diseases is a list of codes developed by the World Health Organization and used to classify various diseases, disorders, health conditions, and causes of death for the purposes of standardizing and using mortality data in different countries and regions. (https://www.who.int/standards/classifications/classification-of-diseases)

defined as diagnosed ADHD, also based on ICD-9 and 10 codes. The authors adjusted for confounding in a stepwise manner. First, the authors adjusted for covariates, including partial proxies for genetic/familial confounding, such as parental lifetime history of mental illness. Second, the authors compared risk among discordantly exposed cousins. Third, the authors compared risk among discordantly exposed siblings. The authors reported a statistically significant increased risk of ADHD when only adjusting for partial proxy factors (adjusted hazard ratio (aHR) 1.86 (95% CI 1.65, 2.10)).[2] The association attenuated but did not disappear in the cousin-controlled analysis (aHR 1.52 (1.12, 2.07)). The authors, however, reported no association in the sibling-controlled analysis (aHR 1.03 (0.76–1.41)). In other words, as the analyses better controlled for genetic/familial factors, the association attenuated and ultimately disappeared. This shows that the association is likely driven by genetic/familial factors, not prenatal infection itself. In this regard, adjustment for proxy factors was insufficient to ensure proper control for genetic/familial confounding.

81. The **Brynge et al 2022** Swedish cohort study evaluated whether prenatal infections were associated with ASD with and without intellectual disability (ID) in children. Maternal infections during pregnancy were ascertained based on ICD codes through the National Patient Register and Medical Birth Register. Outcomes were defined as diagnosed ASD with and without ID from ICD codes, also ascertained through the National and Regional Health Registry. First, the authors reported associations between maternal infection and ASD without ID (aHR 1.27 (1.19, 1.36)) and ASD -with ID (aHR 1.58 (1.37,1.81)) in children. Second, when the authors adjusted for several covariates including partial proxies for genetic/familial confounding such as

[2] Studies discussed in this report used a confidence interval ("CI") of 95% unless otherwise specified. The confidence intervals are reported in parentheses following the risk estimates.

parental psychiatric history, the associations attenuated but were still significant for ASD without ID (aHR 1.15 (1.07, 1.23)) and ASD with ID (aHR 1.35 (1.17, 1.56)). Finally, when the authors conducted a sibling-controlled analysis, the associations further attenuated and became nonsignificant for ASD without ID (aHR 0.89 (0.77, 1.04)) and ASD with ID (aHR 1.20 (0.92, 1.58)). Again, in this example, as the study better controlled for genetic/familial factors, the association attenuated, suggesting that the association was likely driven by genetic/familial factors and not prenatal infection.

82. The Ginsberg and Brynge studies, as well as other studies discussed above, demonstrate that failing to use proper controls for genetic/familial confounding in epidemiological studies of ASD and ADHD can lead to residual confounding. Additionally, these studies illustrate that genetic/familial confounding cannot be fully controlled by adjusting for proxy variables, such as maternal depression or other psychiatric illnesses. For example, controlling or adjusting for a single proxy of genetic/familial risk, such as maternal psychiatric disorder, will not adjust for other maternal genetic contributions, any paternal genetic contribution, or *de novo* genetic mutations. The same limitations apply to analyses that adjust for a PRS since, as noted above, the PRS only considers a portion of total genetic liability. Moreover, even if a study simultaneously adjusts for multiple proxy factors, incomplete or imperfect information about these factors will likely result in residual confounding.

VII.

ACETAMINOPHEN LITERATURE

A. Characteristics of Acetaminophen Users During Pregnancy

83. There is a robust literature demonstrating that (i) mothers who use acetaminophen during pregnancy are different in material respects from mothers who do not; and

(ii) some of these differences are related to the likelihood of having offspring with ASD and ADHD. This literature consists of studies including direct genetic data (such as PRS) and maternal characteristics relevant to potential genetic/familial confounding. These many differences, described in further detail below, will confound results if appropriate controls are not used.

84. The **Leppert et al 2019** study evaluated whether mothers who have higher polygenic risk scores for ASD and ADHD are more likely to use acetaminophen during pregnancy. The study also evaluated whether mothers who have higher polygenic risk scores for ASD and ADHD are more likely to experience certain conditions (e.g., any infection during pregnancy, ever had rheumatism) that may prompt acetaminophen use or conditions (e.g., depression) that acetaminophen users are more likely to experience. The study utilized a dataset from the prospective Avon Longitudinal Study of Parents and Children (ALSPAC) which included 7921 unrelated mothers and 7975 unrelated children of European ancestry. Use of acetaminophen was recorded twice during pregnancy (weeks 18 and 32). Polygenic risk scores were evaluated based on risk alleles associated with ADHD and ASD as of 2019; adjustments for multiple comparisons were made. After adjusting for multiple comparisons, the study reported an association between maternal PRS for ADHD and use of acetaminophen in late pregnancy (odds ratio (OR) 1.11 (1.04, 1.18)), any infection during pregnancy (OR 1.11 (1.04, 1.18)), and ever having severe depression (OR 1.21 (1.11 to 1.33)), but not with acetaminophen use in early pregnancy (OR 1.09 (1.02, 1.17)) and rheumatism (OR 1.05 (0.93, 1.19). The increased odds occurred for each standard-deviation increase in PRS scores. In other words, these risk estimates do not capture the total effect (rather, they only capture increased odds per standard deviation). There was an association between maternal PRS for ASD and ever having severe depression 1.12 (1.02 to 1.23), but not with any

infection during pregnancy (OR 1.06 (0.99, 1.13)), rheumatism (OR 1.16 (1.03, 1.31)), or use of acetaminophen in early pregnancy (OR 1.00 (0.94, 1.08)) or late pregnancy (OR 0.99 (0.93,1.05)).

85. The **Havdahl et al 2022** study, like Leppert, evaluated whether mothers who have higher polygenic risk score for ASD and ADHD are more likely to use acetaminophen during pregnancy. The study also evaluated whether mothers who have higher polygenic risk scores for ASD and ADHD are more likely to experience certain ailments during pregnancy including infections (upper respiratory, lower respiratory, urinary tract), fever, pain, migraine, and headache, which may prompt acetaminophen use and conditions (e.g., depression/anxiety symptoms) that acetaminophen users are more likely to experience. The study used PRS as calculated from 14,539 mothers and 14,897 fathers from the Norwegian Mother and Child Cohort Study (MoBa) prospective cohort. After adjusting for multiple comparisons, lifetime depression was associated with higher maternal PRS scores for ADHD (OR 1.12 (1.08, 1.17)) and ASD (OR 1.12 (1.08, 1.16)), and depression/anxiety symptoms were likewise associated with higher maternal PRS scores for ADHD (OR 1.15 (1.09, 1.22)) and ASD (OR 1.13 (1.06, 1.19)). Other analyses were not statistically significant, although the authors wrote there was "some weak evidence of ADHD PRS and autism PRS association with migraine" and that "migraine could represent a mediating or confounding mechanism between the association of ADHD and paracetamol use." As in Leppert, the authors reported effect estimates for each standard-deviation increase in PRS scores. As with all studies using PRS, the Havdahl study cannot exclude the possibility that there is a genetic link even if an association with a PRS is not observed. The study acknowledges this point: "given that the PGS only explains a small proportion of the variance in the heritability, these estimates do not capture the full extent of genetic confounding.

Consequently, only adjusting for parental PGS in observational studies is unlikely to sufficiently control for genetic confounding."

86. The **Taagaard et al 2023** Danish Copenhagen Pregnancy Cohort study examined prevalence and patterns of acetaminophen use three months prior to pregnancy and in the first trimester of pregnancy in 24,019 pregnancies. Use of acetaminophen prior to and in early pregnancy was significantly higher among women with chronic medical disorders (CMDs) compared to women without CMDs (40.7% versus 35.8% and 9.1% versus 5.1%, respectively). Additionally, women with CMDs were 2.7 times more likely to have frequent acetaminophen intake in pregnancy compared to women without CMDs (aOR 2.69 (2.05, 3.32)). For instance, pregnant women with migraine, rheumatoid arthritis, and mental diseases were significantly more likely to use acetaminophen during pregnancy (aOR 4.39 (3.20, 6.02), aOR 4.32 (2.41, 7.72), and aOR 2.74 (1.67, 4.49), respectively).

87. The **Lupattelli et al 2023** study examined the association of five maternal personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) in pregnant women who took certain medications, including acetaminophen. Using data from the Multinational Medication Use in Pregnancy Study, the authors examined these maternal traits in women who took acetaminophen only once during the pregnancy and those who took acetaminophen in all three trimesters (defined as extended acetaminophen use). The authors noted that women with high neuroticism were more likely to use acetaminophen in all three trimesters during pregnancy (aOR 1.31 (1.08, 1.59). The authors reported, "Having high neuroticism and high social openness were respectively associated with 31% greater and 23% reduced likelihood of extended use of acetaminophen in pregnancy."

88. Additionally, studies that compare maternal background characteristics between the exposed group (pregnant women who use acetaminophen) and control group (pregnant women who do not use acetaminophen) consistently demonstrate that pregnant women who use acetaminophen are more likely to suffer from co-morbidities (e.g., depression) and engage in impulsive behavior (e.g., drinking alcohol, using tobacco products) than pregnant non-acetaminophen users (Bandoli 2020, Stergiakouli 2016, Liew 2016, Inoue 2021, Rifas-Shiman 2020, Vlenterie 2016). For instance, in the Stergiakouli 2016 study, women who took acetaminophen during pregnancy were more likely to have psychiatric illnesses than pregnant non-acetaminophen users (10.2% versus 6.7%). In the same study, pregnant women who took acetaminophen were also more likely to drink alcohol (59.9% versus 53.5%) and more likely to smoke than pregnant non-acetaminophen users (21.3% versus 16.7%) (Stergiakouli 2016). Similarly, Inoue 2021 reported that pregnant acetaminophen users were more likely to have psychiatric illnesses (17.0% versus 13.2%), more likely to drink alcohol (43.4% versus 38.0%), and more likely to smoke (34.4% versus 27.0%) during pregnancy than pregnant non-acetaminophen users.

89. It is also important to note that some of these confounding factors occur in a dose-response fashion among acetaminophen users. In Rifas-Shiman 2020, women who reported progressively higher acetaminophen intake during pregnancy also had a progressively higher prevalence of depression during pregnancy (never took acetaminophen during pregnancy, took acetaminophen once during pregnancy, took acetaminophen 10 times during pregnancy, and took acetaminophen 15 or more times during pregnancy, 8.3%, 8.4%, 10.7%, 11.1%, respectively). Also, women who reported progressively higher acetaminophen intake had a progressively higher prevalence of smoking during pregnancy (never took acetaminophen during pregnancy, took

acetaminophen once during pregnancy, took acetaminophen 10 times during pregnancy, and took acetaminophen 15 or more times during pregnancy, 8.7%, 8.3%, 9.3%, 13.6%, respectively). In Vlenterie 2016, women who took acetaminophen more frequently during pregnancy also drank more alcohol during pregnancy (never took acetaminophen during pregnancy, less than 28 days of acetaminophen use, 28 or more days of acetaminophen, 16.7%, 20.3%, 23.8%, respectively). Additionally, women who took acetaminophen more frequently during pregnancy also smoked more during pregnancy (never took acetaminophen during pregnancy, less than 28 days of acetaminophen use, 28 or more acetaminophen use during pregnancy, 11.7%, 13.5%, 16.2%, respectively). This type of confounding can create a false impression of dose response if the confounding factors are not properly controlled in a particular study.

90. Additionally, evidence suggests that users of acetaminophen during pregnancy are different from those who use acetaminophen after pregnancy. In the Stergiakouli 2016 study, women who took acetaminophen during pregnancy reported an increased likelihood of psychiatric illnesses compared to women who took acetaminophen after pregnancy (10.2% versus 8.1%). In this same study, pregnant women who took acetaminophen during pregnancy were more likely to drink alcohol (59.9% versus 56.4%) and more likely to use tobacco (21.3% versus 18.6%) than women who took acetaminophen after pregnancy (Stergiakouli 2016).

91. In sum, mothers who use acetaminophen during pregnancy are different from mothers who do not take acetaminophen. They are also different from women who use acetaminophen before or after pregnancy. Therefore, designing a study that accounts for all these differences can be difficult. As demonstrated above, statistical adjustments alone can result in residual confounding, and any given study is unlikely to control for all differences between the two groups, which may confound the results. For these reasons, sibling-control study designs,

where the exposed and unexposed groups share the same mothers and familial exposures, are the most effective tool to reduce the potential for known and unknown confounding factors that may influence study results and lead to a spurious association.

B. Epidemiological Studies on Prenatal and Peripartum Acetaminophen Exposure and ASD

92. I reviewed epidemiological studies on maternal use of acetaminophen during pregnancy and the peripartum period and either ASD diagnoses or ASD "symptoms"[3] in children. These studies include those I identified by conducting literature searches on prenatal acetaminophen exposure and ASD outcomes, as well as those discussed in Plaintiffs' experts' reports. None of these studies adequately accounted for confounding by genetics.

93. In total, there are two studies evaluating maternal acetaminophen use during pregnancy and ASD clinical diagnoses in children (Liew 2016, Saunders 2019). One additional study assessed whether acetaminophen use had any effect on the association between maternal fever and ASD (Hornig 2018). Also, there is one study on maternal acetaminophen use during pregnancy and an ASD screening tool, but the children in this study did not have a clinical ASD diagnosis (Avella Garcia 2016). Lastly, there are two studies evaluating maternal acetaminophen use during or shortly after labor and ASD diagnoses (Ji 2018, Ji 2020). Plaintiffs' experts rely on some other studies involving various symptoms but none of them is specific to ASD.

94. The **Avella-Garcia et al 2016** INfancia y Medio Ambiente (INMA) prospective cohort study examined over 2,600 mother/child pairs. Acetaminophen exposure was assessed prospectively by maternal report. A Childhood Autism Spectrum Test (CAST) screening tool was used to assess "ASD symptoms" in 5-year-old children. Such screening tools require

[3] For purposes of this report, I use ASD "symptoms" and ADHD "symptoms" to refer to the outcomes reported in studies which fail to use diagnoses, but instead rely on screening questionnaires and similar instruments.

follow-up with a trained clinician for an ASD diagnosis, which was not performed in this study. Therefore, the clinical relevance of the findings in this study is unclear. In the main analysis, CAST scores were not significant (β 0.08 (-0.28, 0.44)).[4] Moreover, when the authors stratified by gender, while they reported an increase in CAST scores (β 0.63 (0.09, 1.18)) for male children (n=751),[5] they reported a *decrease* in CAST scores (β -0.53 (-0.98, -0.05)) for female children (n=716) whose mothers who took acetaminophen during pregnancy. While the study made several adjustments,[6] none of these adjustments controlled for genetic/familial confounding. The authors acknowledge this limitation by noting: "Other limitations include unmeasured genetic confounding, as ADHD and ASC [ASD] may have genetic components." Additionally, the authors failed to adjust for maternal smoking in pregnancy, despite statistically significantly higher levels of maternal smoking among mothers who took acetaminophen during pregnancy (see Table 1).

95. The **Liew et al 2016** Danish National Birth Cohort (DNBC) prospective study evaluated over 64,000 participants. Acetaminophen exposure was assessed prospectively through maternal report. Outcomes were ascertained through ICD codes from the Danish National Hospital Registry and the Danish Psychiatric Central Registry. The authors reported an increased risk of ASD with co-morbid hyperkinetic symptoms in children (aHR 1.51 (1.19, 1.92)), but no association was found in children with ASD without hyperkinetic features (aHR 1.07 (0.92,

[4] A beta (β) coefficient is used to describe risk estimates which are continuous, as opposed to categorical, in nature. For instance, school grades can be reported as continuous variables (e.g., "80", "81", "82") or categorical variables where a range of scores are grouped together (e.g., "A", "B", "C", "D", etc.). When interpreting a beta coefficient, the value zero (0) represents no effect, so if the confidence interval includes zero, the result is not statistically significant.

[5] In response to criticisms in a published commentary (Ferenci 2017), the authors used two different models to adjust for confounders. Their results for boys remained significant in one model and were no longer significant in another. (Julvez & Avella-Garcia 2017).

[6] The Avella-Garcia et al 2016 study adjusted for covariates such as age at testing, gestational age at birth, gender, maternal social class, IQ, education, chronic illness, fever during pregnancy, and urinary tract infection.

1.24)).[7] The authors reported that, "If ASD and hyperkinetic disorder are considered two different disorders with different etiologies, our results can be interpreted as acetaminophen only having an impact on hyperkinetic disorder but not ASD." Notably, the study did not control for genetic/familial confounding, as the authors were unable to control for "genetics or lifestyle factors." While they did control for certain factors, such as self-reported maternal psychiatric illness, this is not sufficient to control for a large portion of potential genetic factors that can influence the study results. The authors acknowledge this limitation as well: "Despite our efforts to control for a wide range of confounders, the possibility of residual confounding by indication or genetic factors as alternate explanations for our findings cannot be dismissed."

96. The **Hornig et al 2018** Norwegian Mother and Child Cohort Study (MoBa) prospective cohort study evaluated over 79,000 participants. Maternal fever and acetaminophen exposure were assessed prospectively through maternal report. Outcomes were ascertained via ICD codes. The primary analysis evaluated *in utero* exposure to maternal fever and ASD diagnosis, while a secondary analysis assessed whether treatment with acetaminophen altered this association. The study adjusted for several covariates,[8] none of which could control for genetic/familial confounding. In the primary analysis, the authors reported that children exposed to prenatal fever had a significantly increased risk of ASD (aOR 1.34 (1.07,1.67)). In the secondary analysis, the study reported an attenuation of risk estimates for ASD among women who took acetaminophen during pregnancy when compared to women who did not. For instance, the authors reported a significant association in pregnant women with untreated fever in the second trimester (aOR 1.44

[7] The Liew et al 2016 study adjusted for child's sex, birth year, maternal age at birth, parity, socio-economic status, maternal smoking and alcohol drinking during pregnancy, maternal pre-pregnancy body mass index, folic acid intake during pregnancy, mother's psychiatric illnesses, maternal diseases in muscles/joints, fever, or infection /inflammation during pregnancy, maternal use of ibuprofen and aspirin during pregnancy.

[8] The Horning et al 2018 study adjusted for presence of fever in the other trimesters, maternal age, smoking and parity, parental education, and birth year.

(1.02, 2.03)), but this association attenuated and was not significant in pregnant women treated with acetaminophen (aOR 1.37 (0.98, 1.90)) (Supplementary Table S6A).

97. The **Saunders et al 2019** Canadian case-control study examined 215 mothers with children. The study evaluated the presence of environmental exposures, including acetaminophen, in mothers of children diagnosed with ASD. Based on a crude/unadjusted analysis, the authors reported no association between acetaminophen and ASD. Because the authors did not conduct any adjusted analyses for acetaminophen, this finding is uninformative.

98. The **Ji et al 2018** Boston Birth Cohort (BBC) prospective study examined over 1,180 mother/infant pairs. Acetaminophen exposure was assessed prospectively by measuring maternal plasma biomarkers of acetaminophen (unchanged acetaminophen, acetaminophen glucuronide, 3-(N-Acetyl-L-cystein-S-yl and acetaminophen burden) postnatally one to three days after delivery. Outcomes – including ADHD, ASD, and co-occurring ADHD/ASD – were ascertained via ICD codes. Given the two to three-hour half-life of acetaminophen, it is questionable whether the mother was given acetaminophen perinatally or postnatally and the exact time that the mother received acetaminophen was not reported. The authors acknowledged that "maternal acetaminophen can be readily transferred to the fetus through placenta and to the infant via breastfeeding." Overall, the study found no association for ASD and did not adjust for genetic/familial confounding because such data were not collected.[9]

99. The **Ji et al 2020** Boston Birth Cohort prospective cohort study of 996 mother/infant pairs was a follow-up to the Ji 2018 study. Similar to the Ji 2018 study, the authors

[9] The authors adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, drinking during pregnancy, parity, maternal pre-pregnancy, BMI, baby's sex, delivery type, gestational age, and birthweight, maternal fever during pregnancy, and intrauterine infection/inflammation. Of note, the authors did not adjust for maternal pain (e.g., headache, migraine, back pain) despite claiming that they adjusted for the indications of acetaminophen use.

assessed acetaminophen exposure through maternal plasma acetaminophen biomarkers (unchanged acetaminophen, acetaminophen glucuronide, 3-(N-Acetyl-L-cystein-S-yl), and acetaminophen burden) one to three days after birth; however, unlike Ji 2018, the authors also assessed acetaminophen exposure through infant acetaminophen plasma cord levels at birth. Outcomes of ADHD, ASD, and co-occurring ADHD/ASD, in childhood were ascertained via ICD codes. Overall, the authors reported associations with both cord plasma acetaminophen and maternal plasma acetaminophen biomarkers and ASD at the highest exposure category. However, there is no way to determine how much acetaminophen (e.g., one acetaminophen dose, multiple acetaminophen doses) was taken by the mother during pregnancy and/or during labor/delivery based on a one-time infant acetaminophen plasma cord blood level, and the authors do not provide any maternal medication data. The study adjusted for several covariates,[10] and conducted a sensitivity analysis for maternal diagnoses of ADHD, depression, and anxiety, but none of these adjustments allowed the authors to control for genetic/familial confounders because of the study's design. The authors recognized this limitation, stating that "we were unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors." Because it was unclear whether the mothers in this study took acetaminophen during pregnancy, and the study failed to control for known confounding factors such as maternal psychiatric history, this study is uninformative.

100. Lastly, there are two meta-analyses that claim to evaluate whether maternal use of acetaminophen is associated with ASD in children (Masarwa et al. 2018, Alemany et al. 2021). As a preliminary matter, given that none of the underlying studies properly control for

[10] The study adjusted for maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal body mass index, parity, child's sex, delivery type, preterm birth, and low birth weight.

genetic/familial confounding (as discussed above), any meta-analysis will necessarily be confounded as well. Further, neither meta-analysis focused on clinically diagnosed ASD. For these reasons, neither of the two meta-analyses can be relied on to support an association between prenatal acetaminophen use and offspring ASD.

101. In sum, there is no evidence of a reliable or consistent association between maternal use of acetaminophen and the development of ASD in children. Notably, none of the available literature on maternal acetaminophen use and childhood ASD diagnoses or "symptoms" adequately accounted for genetic/familial confounding. Given the lack of a reliable association, there is no basis to reach conclusions about causation.

C. Epidemiological Studies on Prenatal Acetaminophen Exposure and ADHD

102. I reviewed 20 epidemiological studies and five meta-analyses that examined the association between maternal acetaminophen taken during pregnancy (and in certain studies during the peripartum period) and ADHD or ADHD "symptoms" in offspring. These studies include those I identified by conducting literature searches on prenatal acetaminophen exposure and ADHD outcomes, as well as those discussed in Plaintiffs' experts' reports. The 20 epidemiological studies included 17 original maternal acetaminophen usage studies and 3 acetaminophen biomarker studies. Several studies made no attempt to control for genetic/familial confounding, and, therefore, genetic/familial confounding can account for the associations observed in those studies.

1. Studies with Sibling-Controls

103. Among the 20 epidemiological studies, Gustavson et al. 2021 is the only study that evaluated whether maternal acetaminophen use was associated with ADHD clinical diagnoses in children using a sibling-controlled design. Sibling-controlled study design is the best

available and feasible study design to control for genetic/familial confounding in observational epidemiological studies. Another study, Brandlistuen et al. 2013 utilized a sibling-controlled design, but evaluated ADHD "symptoms," not diagnoses. Notably, both studies utilized the same Norwegian Mother and Child (MoBa) cohort and were performed by some of the same investigators but reached different results.

- The **Gustavson et al 2021** cohort study examined over 21,000 children from the Norwegian MoBa cohort. Acetaminophen exposure was assessed prospectively by maternal report. ADHD diagnoses in children were ascertained from ICD-10 codes in 8-year-old children. In the main analysis, the authors reported an increased risk of having a child with ADHD among mothers who used acetaminophen for more than 29 pregnancy days (aHR 2.02 (1.17, 3.25)). However, the association disappeared in the sibling-controlled analysis (aHR 1.06 (0.51, 2.05)), underscoring the strong effect of genetic/familial confounding. The authors also performed a 'family effect' analysis and reported that mothers who took acetaminophen for 29 or more days during one pregnancy have a statistically significant 177% increased risk of having a child with ADHD that carries into future pregnancies, regardless of the mother's acetaminophen use in these pregnancies. This result suggested that unmeasured familial confounding factors could explain the association between long-term maternal acetaminophen use and ADHD in the child.
- The **Brandlistuen et al 2013** Norwegian MoBa prospective cohort study analyzed over 2,900 same-sex sibling pairs. Acetaminophen exposure was assessed prospectively by maternal report. Outcomes included psychomotor development (communication, fine and gross motor development), externalizing and internalizing behavior problems, and

temperament (emotionality, activity, sociability and shyness) in 3-year-old children. The authors reported associations for some but not all outcomes. Additionally, in some instances, associations were only observed with the higher dose group (28 days or more of acetaminophen use) but not with the lower dose group (less than 28 days), and vice versa. The authors reported that "because clinical assessments with diagnostic tools were not available in this study, we could not determine the clinical importance of the difference observed." Finally, the Gustavson et al. 2021 authors commented on this study and stated, "A previous study using the MoBa cohort found an association between maternal acetaminophen use during pregnancy and mother-reported symptoms of externalizing symptoms when the children were three years old (Brandlistuen 2013). Different results in the current study may be due to the use of ADHD diagnoses rather than a maternal report of symptoms, or that children in the previous study were only three years old."

2. Studies with Negative Controls

104. Use of a **negative control** in a study design can help detect uncontrolled confounding if a proper control group is selected. A negative control exposure in epidemiology is typically an analysis that evaluates an exposure that is not expected to be associated with the outcome. For example, in a study looking at whether maternal antidepressant use increases the risk of autism in offspring, one might look at paternal antidepressant use as a negative control. If a negative control analysis reports an association between the exposure and outcome, this casts doubt on other positive findings in the study and suggests that there is unmeasured bias or confounding that may be affecting the study results. However, identifying true negative controls may be difficult. A true negative control exposure should share the same sources of

bias/confounding with the exposure that is being studied, but should not be causally related to the outcome that is studied.

105. Several studies of maternal acetaminophen use and ASD/ADHD have attempted to use negative controls in an attempt to account for residual confounding, including confounding by genetic/familial factors. The negative controls included (i) maternal use of acetaminophen before or after pregnancy and (ii) paternal use of acetaminophen. I discuss those studies below.

- The **Stergiakouli et al 2016** Avon Longitudinal Study of Parent and Children (ALSPAC) cohort study from England examined over 7,700 children. Exposure to acetaminophen was assessed prospectively through maternal questionnaires at 18 and 32 weeks of pregnancy and when the child was 61 months old. Outcomes included behavioral problems using the SDQ total difficulties scale when the child was seven years of age. Surprisingly, in the main text of the publication, the authors reported crude, *unadjusted* risk estimates. *Adjusted* risk estimates[11] (after controlling for a specific set of confounders identified in the study) were reported in the supplemental tables. There was an association between SDQ hyperactivity scores and prenatal acetaminophen exposure reported at 18 weeks (aRR 1.18 (1.01, 1.38)) and 32 weeks (aRR 1.22 (1.04, 1.43)). Notably, however, an even *stronger* association was found between SDQ hyperactivity scores and partner's use of acetaminophen (aRR 1.41 (1.02, 1.97)). No association was found for maternal post-natal use (aRR 1.14 (0.88, 1.49)), but Table 1 shows marked differences between women who used acetaminophen

[11] The authors adjusted for maternal age at birth, parity, socioeconomic status, smoking and alcohol consumption during pregnancy, pre-pregnancy BMI, maternal self-reported psychiatric illness, possible indications for acetaminophen use, and ADHD polygenic risk score as calculated in 2016.

during pregnancy and those who used it postnatally. Issues relating to this study were discussed in several commentaries (Beale et al 2017, Saunders et al 2017, Little et al 2017, Damkier et al 2017). Commentators criticized the authors for various methodological shortcomings such as relying on crude risk estimates and relegating the adjusted (i.e., more reliable) analyses to the supplemental data. Because the supplemental data contradict the authors' conclusions, commentators have suggested that the authors violated publication ethics. Commentators also questioned the clinical significance of the SDQ scores. In response to criticisms, the study authors clarified that, "Regarding clinical significance, we do not claim that our findings are clinically significant or suggest that there should be a change in public health advice following our study, which is explicitly stated in the abstract and discussion."

- The **Liew et al 2019** US Nurse Health Study II (NCE) cohort study evaluated over 8,800 children. Notably, the authors did not have exposure data on maternal acetaminophen use during pregnancy; instead, they assumed that "maternal acetaminophen use (yes/no) reported on the questionnaire during the year of the child's birth" corresponded to maternal acetaminophen use during pregnancy. Outcomes were assessed based on maternal (nurses') self-report of ADHD diagnosis in children who were at least 8 years old. The authors used negative controls by assessing acetaminophen and ADHD associations both pre- and post-pregnancy and compared these associations to acetaminophen use during pregnancy. There was a significant association for acetaminophen use during pregnancy (aOR 1.46 (1.01, 2.09)), but not

before (aOR 1.08 (0.78-1.50)) or after (aOR 0.82 (0.60-1.11)) pregnancy.[12] The authors did not provide any information on whether the women who used acetaminophen before and after pregnancy were similar in terms of background characteristics or potential confounding factors. While this study does not contain this information, the data in Stergiakouli et al. 2016 shows that women who took acetaminophen during pregnancy are different compared to women who took acetaminophen after pregnancy with respect to psychiatric conditions, drinking alcohol, and using tobacco during pregnancy. (Stergiakouli 2016).

- The **Ystrom et al 2017** Norwegian MoBa cohort study included over 112,000 mother/child pairs. Exposure to acetaminophen was assessed prospectively through maternal and paternal questionnaires. ADHD diagnoses were ascertained based on data from the national registry. The authors reported an association between ADHD diagnoses and any maternal acetaminophen use during pregnancy (aHR 1.12 (1.02, 1.24)), but not with maternal acetaminophen use six months before pregnancy (aHR 0.95 (0.85, 1.06)).[13] Notably, the authors reported an even *stronger* association between paternal acetaminophen use six months before pregnancy and ADHD in children (aHR 1.27 (1.08, 1.49)), strongly suggesting genetic/familial confounding.
- The **Chen et al 2019** Taiwanese case-control study examined 950 mother/child pairs. Exposure to acetaminophen was assessed retrospectively via prescription records. Outcomes included ADHD diagnoses ascertained by Taiwan's national insurance

[12] Analyses were adjusted for maternal age, child's birth year, child's birth order, gestational diabetes, preeclampsia, and regular maternal use of aspirin or other nonsteroidal anti-inflammatory drugs at the time of the pregnancy.

[13] The authors adjusted for year of birth, maternal age, parity, co-medication within each indication of use, acetaminophen use first 6 months before pregnancy within each indication of use (first trimester only), and acetaminophen use in the first 6 months postpartum within each indication of use (last trimester only).

database. The authors reported an association between prenatal acetaminophen exposure and ADHD diagnoses (aOR 1.20 (1.01, 1.42)), but not between acetaminophen use during the three months before pregnancy and ADHD (aOR 1.06 (0.90, 1.25)).[14] Again, there was no information about background differences between women before and during pregnancy, which must be considered.

- The **Tronnes 2019** Norwegian MoBa study examined 1791 children prenatally exposed to acetaminophen. Exposure was assessed prospectively based on maternal questionnaires; neurodevelopmental outcome measures were parent reported when children were 5 years old. The two umbrella outcomes assessed included (i) communication and behavioral problems and (ii) temperamental traits. Fourteen comparisons were performed relating to different domains of communication and behavioral problems; the only statistically significant increased risk was reported for acetaminophen use in all 3 trimesters and internalizing problems. Twenty comparisons were performed relating to temperamental traits; the only statistically significant association was a decreased risk of shyness with acetaminophen use in two trimesters. In a negative control analysis (acetaminophen use 6 months prior to, but not during, pregnancy), there was a statistically significant increased risk of communication problems and lower activity levels in children.

3. Studies with Adjustments for Partial Proxies of Genetic Risk

106. Several studies included adjustments for parental mental health disorders (e.g., ADHD, depression), in either the main analysis or in the sensitivity analysis. While these

[14] Analyses adjusted for demographic data, gestational infections, maternal mental health disorders, and comorbid perinatal conditions.

factors are sometimes used as partial proxies for background genetic risk, as noted above, this type of adjustment does not adequately control for genetic/familial confounding because it will not adjust for other maternal genetic contributions, any paternal genetic contribution, or *de novo* genetic mutations.

107. The **Liew et al 2014** et al Danish National Birth Cohort (DNBC) study included over 64,000 children. Exposure to acetaminophen was assessed via prospective maternal report. Outcomes included (1) SDQ total difficulties scores from parental reports; (2) hospital-diagnosed HKD ascertained from a national registry; and (3) use of ADHD medications ascertained from prescription records. The study reported an association between prenatal acetaminophen exposure and SDQ total difficulties scores greater than or equal to seventeen (adjusted relative risk (aRR) 1.13 (1.01, 1.27)), hospital-diagnosed HKD (aHR 1.37 (1.19, 1.59)), and use of ADHD medications in children (aHR 1.29 (1.15, 1.44)).[15]

108. The **Thompson et al 2014** Auckland Birthweight Collaborative cohort study included 871 children. Exposure to acetaminophen was assessed prospectively through parent and child reports. Outcomes included SDQ total difficulties and a Conner's Behavioral Rating Scale scores – based on parental assessment – when the child was seven and eleven years of age. The same outcomes were also assessed via child report at eleven years of age. The study reported an association between prenatal acetaminophen exposure and higher parent reported SDQ

[15] The SDQ analyses adjusted for maternal age at birth, sex of child, child's birth year, gestational age, birth weight, parity, socioeconomic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal pre-pregnancy body mass index, parent's behavioral scores in childhood, mother's ever having had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy. The hospital diagnosed HKD and use of ADHD medications analyses included the same covariates, except that they did not make any adjustment for parent's behavioral scores in childhood.

scores at age seven (β 1.1 (0.2, 2.0)), but not at age eleven (β 0.8 (-0.1, 1.8)).[16] The study also reported an association between prenatal acetaminophen exposure and child reported SDQ scores at age eleven (β 1.1 (0.2, 2.0)). In sensitivity analyses, there was no association for the SDQ hyperactivity subscale for parent-reports at either ages seven (β 0.4 (-0.1, 0.8)) or eleven (β 0.1 (-0.3, 0.6)), or the child-reported hyperactivity subscale at age eleven (β 0.4 (0.0, 0.8)). The authors also reported no associations between prenatal acetaminophen exposure and higher parent reported Conner's scores at age seven (β 1.5 (-0.1, 3.0)) or eleven (β 0.5 (-1.1, 2.1)). In sum, the initial association observed when children were seven was not replicated later when the children were eleven despite using the same screening questionnaire and source.

109. The **Vlenterie et al 2016** Norwegian MoBa cohort study included over 20,000 participants. Exposure to acetaminophen was assessed prospectively through maternal questionnaires. Pregnant women were classified into two acetaminophen exposure groups: short-term acetaminophen use of 1 to 27 days (n=18,962) and long-term acetaminophen use of 28 days or longer (n=1787). Outcomes included psychomotor problems (as assessed by Ages and Stages Questionnaire or ASQ), behavioral problems (as assessed by Child Behaviour Checklist or CBCL), and temperamental problems (as assessed by Emotionality, Activity and Shyness Temperament Questionnaire or EAS) at 18 months of age.[17] None of the outcomes evaluated ADHD or ADHD symptoms specifically. In adjusted analyses, no statistically significant associations were reported

[16] All analyses adjusted for birthweight based on gestational age, sex, age mother left school, maternal smoking during pregnancy, paternal smoking during pregnancy, marital status at birth, parity, socioeconomic status, maternal pre-pregnancy BMI, maternal stress in the last month of pregnancy, alcohol consumption in the first trimester, living with the child's biological father at 3.5 years and child activity levels at age 3.5, high fever during pregnancy, visiting GP for psychological conditions including depression and anxiety, and taking medication during pregnancy for psychological conditions.

[17] These analyses were propensity score-controlled based on maternal age, pre-pregnancy BMI, parity, married/cohabiting, education, smoking, alcohol use, folate use, specific health conditions, psychotropic co-medication and depressive symptoms.

for behavioral problems or temperamental problems. For psychomotor problems, only one of four domains (motor milestones) was significantly associated with more than 28 days of acetaminophen use (Table 2). The authors cautioned that we "should not understate the possibility of chance findings, because we explored a relatively large number of outcomes, which can result in an increased type II error rate. The use of parent-reported behaviour outcomes can also be prone to differential misclassification and do not have simple clinical interpretation. In future studies, more objective neurocognitive and neurobehavioural measures are therefore recommended."

110. The **Liew et al 2016** DNBC prospective cohort study examined over 1,400 mother/child pairs. Exposure to acetaminophen was assessed prospectively through maternal telephone interviews. Outcomes were assessed by psychologists who evaluated each child's attention function using the Test of Everyday Attention for Children at Five (TEACh-5) when the child was 5 years of age. Additionally, parents and preschool teachers completed Behaviour Rating Inventory of Executive Function (BRIEF) to assess executive functions and three composite measures were generated from the subscales: the Global Executive Composite (GEC), the Behavioural Regulation Index (BRI) and the Metacognition Index (MI).[18] In the main analyses, acetaminophen was not associated with the outcome measurements regardless of which measurement or reporter was used. The investigators also performed 120 subgroup analyses, which generated a few statistically significant findings.

111. The **Gustavson et al 2019** Norwegian MoBa prospective cohort study examined over 99,000 children. Exposures (maternal fever and acetaminophen use) were assessed prospectively through maternal reports. Outcomes included diagnosed hyperkinetic disorders

[18] These analyses were only adjusted for parental education, maternal IQ, maternal mental health status, prenatal smoking, prenatal drinking, parity, maternal age at childbirth, child's sex, maternal pre-pregnancy BMI, maternal musculoskeletal diseases, fever or infection/inflammation during pregnancy, and maternal use of ibuprofen or aspirin.

ascertained through ICD-10 codes (mean age: 11 years). Among mothers who experienced a fever during pregnancy, use of acetaminophen did not increase or decrease the risk of ADHD diagnoses as demonstrated by the reported results: fever without acetaminophen (aOR 1.32 (1.01–1.71)), fever with acetaminophen (aOR 1.35 (0.96, 1.90)).[19]

112. The **Rifas-Shiman et al 2020** US (Massachusetts) prospective cohort study examined over 1,200 mother/child pairs. Exposures to acetaminophen and ibuprofen were captured prospectively during the first two trimesters of pregnancy. Outcomes included executive functioning scores (measured by the BRIEF questionnaire) and behavioral scores (measured by the CBCL questionnaire). Questionnaires were completed by both parents and teachers when children were in mid-childhood (median age of 8 years old). The authors reported several associations for both acetaminophen and ibuprofen,[20] in the context of more than 130 comparisons and without adjusting for multiple testing. In a sensitivity analysis (eTable 5), the associations were strongest among children whose mothers used both acetaminophen and ibuprofen, suggesting that the results were driven by confounding factors.

113. The **Inoue et al 2021** DNBC cohort study included over 40,000 children. Exposure to acetaminophen was ascertained prospectively during and after pregnancy through maternal reports. The outcomes measured were higher SDQ scores, including the hyperactivity subdomain, reported by both the parent and child when the child was eleven years old.[21] There

[19] Analyses were adjusted for maternal age, maternal educational level, parity, maternal pre-pregnancy BMI, maternal pre-pregnancy psychological and psychiatric problems, maternal ADHD symptoms, maternal smoking, and child's birth year.

[20] Analyses were adjusted for maternal age, education, smoking, parity, and antibiotics, antidepressants, and depression during pregnancy; household income and HOME score; and child age, sex and race/ethnicity.

[21] Analyses adjusted for maternal age at birth, child's birth year, parity, socio-occupational status of mother, maternal pre-pregnancy body mass index, maternal smoking, alcohol drinking during pregnancy, mother's ever having had mental health problems, maternal diseases in muscles/joints, fever or infection/inflammation during pregnancy, and NSAIDs intake during pregnancy.

was an association between prenatal acetaminophen exposure and increased SDQ Hyperactivity scores reported by the parent (aRR 1.12 (1.02, 1.24)) and child (aRR 1.18 (1.08, 1.29)).

114. The **Sznajder et al 2022** First Baby Study (Pennsylvania) prospective cohort study included over 2,400 mother/child pairs. Acetaminophen exposure was ascertained prospectively once during the third trimester of pregnancy. Outcomes were assessed by the parent-reported CBCL checklist when children were 3 years old. The CBCL scores were divided into several domains: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, and attention. The authors reported an association between prenatal acetaminophen exposure and higher CBCL attention scores at three years old (aOR 1.21 (1.01, 1.45)).[22]

4. Studies with No Attempts to Adjust for Genetic Risk

115. The following acetaminophen studies (Avella Garcia 2016, Tovo-Rodriques 2018, Ji 2018, Golding 2020, Ji 2020, Baker 2020), did not attempt to control for genetic/familial covariates through a sibling design, a negative control, or by adjusting for parental mental health (e.g., ADHD, depression). As a result, their findings are even more limited than those discussed in the section above, and residual confounding is very likely.

- **Avella Garcia et al 2016** is described above. Attention-related "symptoms" were assessed through an ADHD-DSM-IV symptom scale and Conner's Kiddie Continuous Performance Test (K-CPT) Omission and Commissions test in children at 5 years of age. In the main analysis, the associations were insignificant for ADHD-DSM IV total symptoms (aRR 1.25 (0.93, 1.69)), inattention symptoms (aRR 1.12 (0.79, 1.58)), and K-CPT-Omission Errors (aRR 0.98 (0.89, 1.08)). Significant associations were

[22] This analysis was adjusted for trouble sleeping, thyroid conditions, maternal age, insurance coverage, alcohol consumption, diagnosis of anxiety or depression and stress.

reported for hyperactivity/impulsivity symptoms (aRR 1.41 (1.01, 1.98)) and K-CPT-Commission Errors (aRR 1.10 (1.03, 1.17)).[23] In response to criticisms in a published commentary (Ferenci 2017), the authors used two different models to adjust for confounders. In both of these models, the results for hyperactivity/impulsivity symptoms became attenuated and no longer significant (Julvez & Avella-Garcia 2017).

- The **Tovo-Rodriques et al 2018** Brazilian Pelotas prospective cohort study evaluated over 3,000 children. Exposure to acetaminophen was assessed via prospective maternal report. Outcomes were assessed based on an SDQ scale in children at 6 and 11 years of age. The SDQ scale was divided into five domains: inattention/hyperactive symptoms, conduct problems, emotional symptoms, peer relationship problems, and prosocial behavior. In the main analysis, the SDQ hyperactivity/inattention associations were insignificant at 6 and 11 years of age (aOR 1.10 (0.87, 1.39)) and (aOR 1.20 (0.96,1.49)), respectively.[24] When the authors stratified by gender, a statistically significant association was reported in boys at age 6 (aOR 1.42 (1.06, 1.92)); however, this association was no longer statistically significant by age 11 (aOR 1.25 (0.95, 1.65)). There was no statistically significant association in girls at 6 years of age (aOR 0.76 (0.51,1.12)) and at 11 years of age (aOR 1.14 (0.79, 1.64)).
- The **Golding et al 2020** Avon Longitudinal Study of Parents and Children (ALSPAC) prospective cohort study examined over 14,000 children. Exposure to acetaminophen

[23] This analysis was adjusted by regional cohort, child gender, age at testing, gestational age at birth, and maternal social class, education, IQ, chronic illness, fever during pregnancy, urinary infection during pregnancy, use of any other medication; however, K-CPT outcome model was not adjusted for use of any other medication.

[24] Analyses adjusted for sex, maternal age, parity, national economic index, maternal educational level, smoking during pregnancy, alcohol consumption during pregnancy, maternal skin color, infection during pregnancy, pre-gestational BMI, presence of maternal mood issue, and use of other analgesics during pregnancy.

was assessed prospectively via a maternal report. The authors evaluated 135 separate continuous outcomes, increasing the likelihood of statistically significant findings that were simply the result of chance; an adjustment for multiple comparisons was performed. Outcomes included attention and excessive activity using SDQ at various ages from 3 to 11 years via both maternal and teacher reports and from the Development and Well-being Assessment (DAWBA) series of questions answered by mothers and teachers when the children were 7 to 8 years of age. While the authors reported some associations between acetaminophen use and hyperactivity in younger children, these associations were no longer observed among older children (e.g., eTable 5, showing statistically significant associations with hyperactivity at 42 and 47 months, but not at 81 months or any time thereafter, up to 10-11 years old).[25] The authors also reported associations between DAWBA attention scores at age 7-8, but this outcome was not analyzed at age 10-11 like hyperactivity was. The authors concluded that prenatal acetaminophen use "was associated with adverse trends in pre-school child behaviour, but the associations were no longer present by the end of primary school (age 10-11 years)."

- The **Parker 2020** longitudinal study examined approximately 1,100 children. Exposure to acetaminophen was ascertained through maternal recall after birth but prior to childhood neurodevelopmental assessments. Outcomes were assessed through maternal report of the Child Behaviour Checklist (CBCL) and teacher report of the Teacher Report Form (TRF). Differences between the exposed and unexposed groups

[25] Analyses adjusted for maternal asthma, indigestion, back pain or migraine, pre-pregnancy BMI, subjective assessment of health in late pregnancy, having a cold, flu, an infection or a headache in late pregnancy, healthy diet score, processed diet score, alcohol consumption in pregnancy, domestic cleaning chemical score, and parity.

were reported as risk ratios and mean differences per one standard deviation. There were no associations with mother-reported or teacher-reported outcomes in the most adjusted models (i.e., those additionally adjusted for indication). In the least adjusted models,[26] there were some associations with mother-reported outcomes, but not with teacher-reported outcomes. The authors reasoned that since these associations were observed when children's behaviors were reported by mothers, but not teachers, relying on maternal reporting of behaviors may introduce dependent (i.e., differential) misclassification which would bias towards a spurious increased risk.

- **Ji et al 2018 and Ji et al 2020.** Notably, I discussed the limitations of **Ji et al 2018** and **Ji et al 2020** in the acetaminophen/ASD section above (**Section VII-B**), and those limitations apply equally here. The **Ji et al 2018** authors reported associations between plasma maternal acetaminophen biomarkers and ADHD in children. The **Ji et al 2020** authors reported associations with both cord plasma acetaminophen and maternal plasma acetaminophen biomarkers and ADHD at the highest exposure category. In both studies, it is unclear when the mothers took acetaminophen (e.g., during pregnancy or during labor and delivery), and there was no attempt to control for genetic/familial confounding.
- The **Baker et al 2020** Quebec prospective study examined 345 infants. Acetaminophen exposure was assessed via acetaminophen infant meconium biomarkers. Outcomes were ADHD diagnoses based on parental report and medical records in 6- to 7-year-old children, as well as based on magnetic resonance imaging (MRI) and a Behavioral

[26] These least-adjusted models were only adjusted for maternal age, race, education, marital status, smoking, drinking, and parity.

Assessment System for Children Parent Report Scale (BASC3-PRS) when the children were older at 9 to 11 years old. Acetaminophen was detected in 199 meconium samples, and ADHD was diagnosed in 33 children. The authors reported an association between acetaminophen in meconium and ADHD (OR 2.43 (1.41, 4.21)). However, the sample size was small, and it is unclear whether the newborn meconium acetaminophen sample reflected maternal acetaminophen given during pregnancy, when breastfeeding the child, or if the neonate received acetaminophen prior to the meconium collection.

- Although all three biomarker studies reported associations between acetaminophen biomarkers and ADHD, the findings are severely limited because of the investigators' inability to pinpoint the timing of exposure (e.g., during or after pregnancy) and lack of adjustments for genetic/familial factors.

5. Meta-Analyses

116. Finally, I examined five meta-analyses that evaluated maternal use of acetaminophen and ADHD in children (Masarwa et al 2018, Gou et al 2019, Alemany et al 2021, Masarwa et al 2020, Ricci et al 2023). While all the meta-analyses reported associations between maternal acetaminophen use and ADHD, they are severely limited in multiple respects:

- All of the meta-analyses included studies that did not properly control for genetic/familial confounding.
- None of the meta-analyses focused on the association between prenatal acetaminophen exposure and diagnosed ADHD. For example, in **Masarwa et al 2018**, only one of the six studies that were pooled included children with an ADHD clinical diagnosis, and the remaining studies used various ADHD screening tools.

- The meta-analyses included studies that failed to adjust for key confounding factors, such as parental mental health. For example, in a re-analysis of their 2018 meta-analysis, the **Masarwa et al 2020** authors showed that adjustment on parental ADHD and maternal migraine shifted the point estimates towards the null. The authors wrote: "Parental ADHD and maternal migraine were not adjusted for in some published studies, and these variables may play a crucial role in the observed association."

6. Analysis

117. Across the ADHD epidemiology on prenatal acetaminophen exposure, there are common methodological limitations and findings that preclude finding an association not likely to be due to chance, bias, and/or confounding. Some of the most prominent and pervasive limitations are discussed below.

118. First, virtually none of the studies adequately control for genetic/familial confounding even though ADHD is a highly genetic and heritable disorder. Pregnant acetaminophen users, and their families, tend to have a higher genetic/familial risk of giving birth to a child ADHD. This background risk is demonstrated across different types of studies, including those utilizing sibling-controls, polygenic risk scores, and negative controls, as well as studies that report the distribution of characteristics of pregnant acetaminophen users compared to pregnant non-users.

119. Only two studies involved a sibling-control design, and only one of these evaluated clinically diagnosed ADHD. That study (**Gustavson et al 2021**) demonstrated that once genetic/familial confounding is taken into account, the association between prenatal exposure to acetaminophen and ADHD disappears.

120. In **Brandlistuen et al 2013,** a sibling-controlled analysis did not fully attenuate the risk estimates, but – unlike Gustavson et al 2021 – that study did not evaluate clinically diagnosed ADHD. The authors wrote: "we could not determine the clinical importance of the difference observed. Future studies should seek to include clinical diagnoses of neurodevelopmental and behavioural diagnoses, to explore whether there is an increased risk of, for example, attention deficit hyperactivity disorder (ADHD)." These investigators ultimately conducted a follow-up investigation, using clinically diagnosed ADHD as an endpoint in the Gustavson 2021 study, and reported no association. Because the Gustavson study used clinical diagnoses of ADHD, its findings supersede the findings reported in Brandlistuen.

121. By contrast, most other studies failed to adjust for genetics at all, even when the same cohort was subject to multiple studies over time. For example, three studies (**Liew et al 2014**, **Liew et al 2016**, **Inoue et al 2021**) were published by many of the same authors using the same data set, the Danish National Birth Cohort, but none of these studies properly controlled for genetic/familial confounding through a sibling-controlled design. Indeed, the authors themselves admitted that genetics may confound the reported associations and suggested the use of a sibling-controlled design (Olsen & Liew 2016, Reply to Avella-Garcia).

122. Several studies utilized negative controls, such as (1) partner's acetaminophen use and (2) maternal use of acetaminophen when not pregnant. These negative controls underscore the importance of controlling for genetic and familial factors.

- Partner's (paternal) use of acetaminophen was associated with ADHD or other behavioral outcomes in children in both studies where it was analyzed (Stergiakouli 2016, Ystrom 2017). Indeed, the risk estimates were higher for paternal than for maternal exposure, and there was evidence of dose response. This suggests that

genetic/familial factors are likely to be confounding any associations observed between prenatal exposure to acetaminophen and ADHD.

- Maternal use of acetaminophen when not pregnant was not associated with an increased risk of ADHD in several analyses (Ystrom 2017, Liew 2019, Chen 2019). However, this type of a negative control analysis does not argue against genetic/familial confounding because (as I discuss extensively above) women who use acetaminophen during pregnancy are fundamentally different from women who use acetaminophen outside of pregnancy (Stergiakouli 2016, Taagaard 2023). Significantly, the authors of Ystrom 2017, Liew 2019, and Chen 2019 did not evaluate whether the exposure group and negative control group had differences in background characteristics. Therefore, there is no evidence that genetic/familial characteristics were similar between the exposed and negative control groups.

123. Additionally, some of the studies adjusted for partial proxies of genetic/familial risk such as maternal ADHD diagnoses or maternal depression, but as discussed in **Section VII.C.3**, these types of controls have been demonstrated to be insufficient to reliably account for genetic confounding.

124. Second, many studies conducted multiple independent analyses, which increase the likelihood of generating statistically significant results by chance alone. With a p-value of 0.05, one out of 20 comparisons will generate a statistically significant result by chance alone. Therefore, when a study conducts numerous analyses, the use of a lower p-value may be necessary to account for the likelihood of false-positive findings. Two studies acknowledge the need to adjust for multiple comparisons (Brandlistuen 2013, Golding 2020). The Brandlistuen study used a p-value of 0.01, and the Golding study used a p-value of 0.0001. The remaining

studies, however, made no attempt to correct for multiple comparisons. Therefore, statistically significant results in the context of multiple comparisons should be interpreted with caution.

125. Finally, as discussed earlier in this report, a significant portion of the literature does not study clinically diagnosed ADHD. As a result, the study authors themselves often acknowledge that the clinical significance of results is unclear.

126. These limitations illustrate the significant flaws in the existing literature, all of which (whether considered separately or collectively) preclude a causal inference from the available data.

VIII.

RESPONSE TO PLAINTIFF EXPERT REPORTS

A. Role of Genetics in the Etiology of ASD and ADHD

127. Dr. Hollander and Dr. Baccarelli's reports attempt to diminish the role of genetics in the etiology of ASD and ADHD. In his report, Dr. Hollander acknowledges that "genes account for up to about 85 percent of autism's heritability" (Dr. Hollander Amended Report, p. 18). However, he then writes that "only about 10 percent of individuals with ASD have an identifiable genetic cause" (Dr. Hollander Amended Report, p. 18). Dr. Baccarelli also acknowledges that "more than 800 genes" are currently found associated with ASD, but then states "no single genetic etiology accounts for more than 0.2% of cases among individuals with non-syndromic ASD" (Dr. Baccarelli Amended Report, p. 42). Although we do not yet know the full architecture of genetics and thus do not yet know all the genes or genetic variants and their roles in ASD and ADHD, it is well established that genetics play a critical role in causing these conditions. Drs. Hollanders and Baccarelli neglect to acknowledge that there are rare inherited variants and *de novo* variants, which are highly penetrant. These rare inherited variants and *de*

novo variants are estimated to account for approximately 50% of the genetic etiology of ASD and common inherited genetic variants account for approximately one third of ADHD's heritability (Yang 2013, Faraone 2019, Demontis 2023). Further, the heritability calculations do not account for *de novo* mutations. For these reasons, the referenced statements about the genetic contribution to ASD and ADHD etiology are incomplete and can be misleading.

B. No Established Reliable Data Exist for Gene-Environment Interaction between Acetaminophen and ASD and ADHD

128. Drs. Baccarelli, Cabrera, Louie, and Pearson assert that maternal acetaminophen intake can exert gene-environment interactions and can cause changes in genetics that lead to the development of ASD and ADHD (Dr. Baccarelli Amended Report, p. 42; Dr. Cabrera Amended Report, pp. 176-77; Dr. Louie Amended Report, pp. 71-73; Dr. Pearson Amended Report, p. 39). They propose the following hypothetical mechanisms for how this might work: 1) epigenetics, 2) altering genetic expression in certain biological pathways for ASD and ADHD, 3) alteration of gene expression related to ASD and ADHD, 4) DNA damage, and 5) individual susceptibility to acetaminophen toxicity.

1. Epigenetics

129. Drs. Baccarelli, Hollander, Louie, and Pearson opine that maternal acetaminophen intake can alter epigenetic profiles, such as DNA methylation, in fetal tissues, leading to differential expression of genes that relate to the development of ASD and ADHD (Dr. Baccarelli Amended Report, pp. 48-50; Dr. Hollander Amended Report, pp. 83-86; Dr. Louie Amended Report, pp. 67-71; Dr. Pearson Amended Report, p. 60). The principal studies cited for this argument are as follows:

- Gervin et al. 2017 is an epigenome-wide association study (EWAS) that examines a genome-wide set of quantifiable epigenetic marks, such as DNA methylation, among

individuals with various phenotypes to derive associations between epigenetic variation and a particular phenotype. Cord blood from 384 individuals in the Norwegian Mother and Child Cohort (MoBa) was analyzed for DNA methylation. Differences in DNA methylation were observed between children diagnosed with ADHD and controls and between infants prenatally exposed long-term to acetaminophen (>20 days) (usually across all three trimesters) and those not exposed to acetaminophen. Of the top ranked genes with differential methylation, some were linked to oxidative stress, neural transmission, and olfaction. Information about prenatal usage of acetaminophen was obtained through questionnaries.

- Spildrejorde et al. 2022 is an *in vitro* study using human embryonic stem cells (hESCs) conducted by the same group as Gervin et al. 2017. hESCs undergoing neuronal differentiation were exposed to acetaminophen at day 7 and 20, and DNA methylation changes as well gene expression were examined. The authors reported that methylation and gene expression were altered upon exposure to acetaminophen, and the differentially methylated and/or expressed genes were involved in multiple pathways, such as neurotransmission, cell fate, and deamination.
- Eslamimehr et al. 2022 is also an EWAS study. Data from three consecutive generations of the Isle of Wight cohort were analyzed to evaluate whether differences in DNA methylation patterns in newborns were associated with prenatal use of acetaminophen. Information about prenatal use of acetaminophen was obtained through analysis of maternal serum and questionaries. Out of >850,000 cytosine-phosphate-guanine sites (CpGs) where DNA methylation occurs, 11 sites (0.0013%)

were found to be differentially methylated with prenatal acetaminophen use in two generations.

130. These three studies do not demonstrate that maternal intake of acetaminophen causes ASD or ADHD in offspring through a mechanism of epigenetics. Epigenetic chemical modifications change over time and can be secondary and as a result of a person's specific condition rather than primary and a cause of the condition. For example, some individuals with ASD may have cravings for things that are non-food (a condition known as pica) or restrictions in food choices based upon the textures of the food or their preferences for the same limited groups of foods. As a result, these individuals may develop epigenetic profiles secondarily reflective of their diets rather than primarily reflecting the cause of ADHD or ASD.

131. The observed changes also do not inform the etiology of ASD and ADHD because of the tissue/cells assessed and timing of the observed epigenetic changes. ASD and ADHD are neurodevelopmental conditions that affect the brain and, therefore, epigenetic changes need to be observed in the brain or neuron. Further, there is a critical period for the development of ASD and ADHD, and the observation must be performed at the relevant time period, including the prenatal period if the question is regarding prenatal exposures and impact on the brain and behavior. The epigenetics studies performed on human cord blood samples or newborns' dried blood spots do not reflect samples at the relevant time or tissue. Spildrejorde et al. 2022 attempted to assess developing brain cells, but the experiments were performed *in vitro*, and it is unclear whether this *in vitro* model or the culture conditions used properly mimic the human developmental process.

132. Epigenetic results are also difficult to reproduce. Olstad et al. 2023 is a study performed by the same research group that published Gervin et al. 2017 and Spildrejorde et

al. 2022. In Olstad et al. 2023, the authors attempted to replicate Gervin et al. 2017 by increasing the sample numbers, but instead identified "no impact of paracetamol nor interaction of paracetamol and FA [folic acid] on cord blood DNAm [DNA methylation] in children with ADHD" in their data and stated that they "did not replicate [their] previous results (Gervin et al., 2017)." The authors acknowledged the evolution of sequencing technology as a possible reason for failure in replication.

2. Gene Expression Alteration Involved in Certain Biological Pathways

133. Drs. Cabrera and Pearson assert that maternal acetaminophen intake can lead to gene expression alterations involving disruptions in certain biological pathways, such as oxidative stress (e.g., Baker 2023), disruption of prostaglandin synthesis (e.g., Dean 2012), endocrine disruption (e.g., Lichtensteiger 2015), toxic NAPQI (e.g., Jetten 2012), and endocannabinoid signaling dysfunction (e.g., Philippot 2018). These experts cite the following studies, among others:

- Jetten et al. 2012 is a study of human blood and urine samples after postnatal exposure to acetaminophen. Healthy adult subjects orally took 0.5, 2 or 4 g of acetaminophen over 24 hours and blood and urine samples were collected at various time points within the 24 hrs. Upon examining gene expression, changes were observed in genetic pathways related to immune responses (2 g dose) and oxidative stress responses (4 g dose). The authors state that the acetaminophen metabolite NAPQI which is produced in the liver after overdoses is responsible for oxidative stress.
- Dean et al. 2012 is a rat study investigating the effect of postnatal prostaglandin synthesis inhibitors, including acetaminophen, in the cerebellum. From Post Natal Day (PND) 7 to PND13 daily, male and female rat pups were treated once per day with

subcutaneous injections of acetaminophen (40 mg/kg) or other synthesis inhibitors. The authors reported acetaminophen altered development of Purkinje cells and increased the amount of dendrite spines related to the protein spinophilin in the cerebellum of PND 14 rat pups.

- Lichtensteiger et al. 2015 is a rat study testing the prenatal effects of acetaminophen and other endocrine disrupting chemicals on gene expressions in the developing brain. Animals received either a mixture of endocrine disrupting chemicals with or without acetaminophen at various concentrations or acetaminophen alone (360 mg/kg/day). Dams were dosed with acetaminophen alone by oral gavage from Gestational Day (GD) 13 to GD 19 and after birth from PND 14 to PND 22, and with mixture by oral gavage from GD 7 to PND 21 and after birth from PND 1 to PND 22. Gene expression was analyzed at PND 6 in certain areas of the brain (medial preoptic area (mPOA) and ventromedial hypothalamus (VMH)). For samples with acetaminophen alone, alteration in expression was observed for the genes that were anti-androgenic in the peripheral nervous system although general developmental endpoints were not affected by acetaminophen treatment.
- Philippot et al. 2018 is a mouse study testing the effect of early postnatal exposure of acetaminophen and cannabinoid receptor type 1(CB1R) agonist. Male mice (at PND 10) were subcutaneously injected with (1) a saline vehicle, (2) acetaminophen (30 mg/kg) of single or double dose, (3) CB1R agonist (1 mg/kg, single dose), (4) a combination of acetaminophen/CB1R agonist (30 mg acetaminophen/1 mg / kg) of single or double dose. Only co-exposure to acetaminophen and CBR1 agonist displayed a significant lack of habituation in the spontaneous behavior test.

Expressions of several genes related to neurons, synapses, and endocannabinoid were analyzed and several downregulated genes include: (1) Trkb (a BDNF receptor), (2) Faah (an enzyme to hydrolyze endocannabinoid anandamine) and (3) Syp (a synaptic protein).

- Koehn et al. 2020 is a rat study testing effects of acetaminophen during pregnancy on gene expression in the fetal brain and placenta. Embryos of a pregnant dam were given an intraperitoneal injection twice daily of 15 mg/kg of acetaminophen from Embryonic Day (ED) 15 to ED 19 (chronic) or as a single dose at ED 19 (acute). The authors reported a large number of RNA expression changes from acutely or chronically treated animals including upregulation of immune-response and inflammation related genes in both placenta and brain at ED 19.
- Baker et al. 2023 is a mouse study testing the effect of prenatal acetaminophen exposure on behavior as well as gene expression in the brain. Pregnant mice (ED 4-10) were orally exposed to acetaminophen (150 mg/kg/day) through PND 14. In addition to performing behavioral tests, such as open field test, pup ultrasonic vocalization, and pre-pulse inhibition, gene expression in the prefrontal cortex at birth was analyzed. Sex-specific differences in expression of 10 genes were reported. Upon performing gene enrichment analysis, pathways involving glutathione, cytochrome p450 metabolism, DNA damage, endocrine and immune systems were found to be altered.

134. These studies do not support that maternal acetaminophen intake can cause ASD and ADHD in the offspring through changes in the gene expression involving the referenced biological pathways. The genes reported to be differentially expressed are not known to be risk genes for either ASD or ADHD. I am also not aware that the referenced biological pathways are

established or accepted by the medical and scientific community as causal mechanisms for ASD or ADHD.

135. In addition to these limitations, animal models do not measure phenotypes corresponding to ASD or ADHD. Mice/rats do not have equivalent behaviors to human ASD or ADHD, and rodent development and physiology differ from humans. Further, extrapolating from the large doses used in most rodent studies to humans is challenging. Therefore, it is impossible to correlate any changes in gene expression in animals with ASD or ADHD features.

136. The observed changes also do not inform the etiology of ASD and ADHD because the tissues sampled and the time they were sampled and assessed for gene expression changes are not relevant to human brain development which is largely prior to birth.

3. Alteration of Gene Expression Related to ASD And ADHD

137. Drs. Baccarelli, Cabrera, Hollander, and Louie also hypothesize that maternal intake of acetaminophen makes individuals susceptible to ASD by altering the expression of autism susceptibility genes. One of the studies on which they rely is Carter et al. 2016 (Dr. Baccarelli Amended Report, p. 49; Dr. Cabrera Amended Report, p. 176; Dr. Hollander Amended Report, pp. 83-85; Dr. Louie Amended Report, pp. 71-72).

138. Carter et al. 2016 is a database analysis study. No experimental studies were performed. Using 206 autism susceptibility genes, the Comparative Toxicogenomics Database was assessed for interactions between chemical and genes or proteins. Among the 206 genes, the authors reported that 92 genes were affected by acetaminophen.

139. Carter et al. 2016 does not provide any experimental evidence regarding environmental exposure (e.g., frequency, amount, and timing) and purported changes in gene expression (e.g., location and timing). This was a general study assessing many environmental

exposures, and there is little specificity in this analysis of acetaminophen and likely large numbers of false positives given the number of combinations of associations tested. Therefore, the results cannot be interpreted as analyzing any potential effect for developing ASD and ADHD from acetaminophen exposure.

140. I am also not aware of any study demonstrating changes in gene expression related to ASD and ADHD in the brain/neuron at the physiologically relevant time period.

4. DNA Damage

141. Drs. Cabrera, Louie, and Pearson assert that acetaminophen damages DNA sequences and increases the risk for leukemia (Dr. Cabrera Amended Report, pp. 74-75; Dr. Louie Amended Report, pp. 48, 65; Dr. Pearson Amended Report, pp. 60-61). Dr. Pearson states that acetaminophen results in oxidative damage through one of its metabolites (NAPQI) leading to DNA damage (Dr. Pearson Amended Report, p. 55).

142. Cancer is the disease most commonly associated with somatic DNA damage. Acetaminophen is one of the most commonly used drugs in the world and is designated by the World Health Organization as an "Essential Medicine." Recent comprehensive assessments of published data found no reports of carcinogenesis or increased cancer risk with acetaminophen use (Kirkland 2021, Murray 2020). I am not aware of any study reporting that recommended doses of acetaminophen damages DNA. Acetaminophen is so widely taken in the general population that if there were an increased risk of DNA damage, there would have been reports of increased cancer frequency (likely of epidemic scope) in the general population of individuals who regularly take acetaminophen.

5. Individual Susceptibility to Acetaminophen Toxicity

143. Dr. Pearson writes that genetic (and non-genetic) susceptibility to "APAP-induced toxicity" can affect acetaminophen metabolism and disposition. He therefore concludes that epidemiological studies are unable "to fully account for interindividual differences in APAP toxicity" (Dr. Pearson Amended Report, p. 14). Dr. Cabrera cites a study that reports less methylation in the placenta of children with ASD, which leads to elevated CYP2E1 expression in the prenatal human brain (Dr. Cabrera Amended Report, p. 60). The authors rely on the following studies, among others:

- Harrill et al. 2009 is a mouse study analyzing genetic polymorphisms to identify candidate genes for acetaminophen-induced liver injury sensitivity. The study reports that certain polymorphisms in two genes (CD44 and CAPN10) were associated with elevation in serum ALT, which is a marker for liver injury. The study then tested corresponding polymorphisms in CD44 and CAPN10 in humans. The study suggests an association with elevated ALT with the polymorphism in CD44 and only a trend that was not statistically significant for ALT elevation with a polymorphism in CAPN10.
- Krasniak et al. 2014 is a review article summarizing the variability of acetaminophen metabolism profiles observed between adults and children as well as among pediatric populations. The authors discuss several studies reporting potential genetic variability that could explain the differences.
- Zhu et al. 2019 analyzed methylation status of placentas from high-risk pregnancy mothers in the MARBLES (Markers of Autism Risk in Babies- Learning Early Signs) study. Placentas of mothers whose children were later diagnosed with ASD were

reported to have decreased DNA methylation of CYP2E1, a gene that is involved in acetaminophen metabolism, when compared to the placentas of mothers whose children were not diagnosed with ASD, which suggested potential increase in CYP2E1 expression. However, the study failed to find a statistically significant difference in CYP2E1 protein levels within the placentas between mothers whose children had ASD and mothers whose children did not have ASD.

- Santos et al. 2022 is a literature review and database analysis. The authors identified 77 genes whose genetic variants might cause less efficient detoxification capacity of substances foreign to the organism (xenobiotics). They then searched the Comparative Toxicogenomics Database to report "gene-environmental interactions" for these genes. The authors speculate that altered levels of xenobiotics for individuals with the susceptible genetic variants could be associated with increased ASD risk. No data are shown, and acetaminophen is not mentioned specifically as one of the xenobiotics examined.

144. These studies offer only speculation about individual susceptibility to acetaminophen as a cause of ASD or ADHD. Neither large-scale genetic studies focusing on ASD, ADHD, and other neurodevelopmental disorders (e.g., de Rubeis 2014, Grove 2019, Hamanaka 2022, Demontis 2023) nor international genetic databases (e.g. Simons Foundation Autism Research Initiative (SFARI) Gene, Developmental Brain Disorder (DBD), Deciphering Developmental Disorders (DDD)) report a gene involving acetaminophen metabolism, including CYP2E1, as an ASD risk gene. I am not aware of any such data, either.

C. Sibling Controlled Designs

145. Dr. Baccarelli asserts that sibling-controlled designs can lead to bias, resulting in falsely attenuated associations. Specifically, he argues that familial/genetic effects could act as a mediator or effect modifier in the association between acetaminophen and ADHD. However, he does not provide any examples of specific family/genetic effects that purportedly act as mediators or effect modifiers, nor does he explain how such effects would lead to an artificial attenuation of the risk.

146. Instances where a sibling-controlled design would bias the association toward the null are very rare and typically require that exposure in the first pregnancy influence the outcome in the second pregnancy (Sjolander 2016). For example, fetal breech in the first pregnancy increases the risk of C-section in the first pregnancy and in subsequent pregnancies (Macharey 2020). Therefore, a sibling-controlled analysis of fetal breech and C-section may understate the true association.

147. Dr. Baccarelli does not identify a basis for asserting that maternal acetaminophen use in the first pregnancy influences ADHD outcomes in subsequent pregnancies. Nor does he provide any other scientific evidence that a sibling-controlled study would bias the results toward the null. Gustavson 2021 specifically considered the possibility that having a child with ADHD in the first pregnancy would influence the use of acetaminophen during subsequent pregnancies; yet, they found no evidence of this in their dataset (Supplemental Analysis 2.4.1.; "this did not provide evidence of carryover effects from sibling one's ADHD diagnosis to sibling two's acetaminophen exposure."). Dr. Baccarelli provides nothing but speculation that sibling-controlled analyses in studies of acetaminophen and ADHD underestimate true associations.

IX.

CONCLUSION

148. For the reasons described in this report, I conclude that (i) genetics are the predominant cause of ASD and ADHD; and (ii) there is insufficient scientific evidence to support the conclusion that maternal intake of acetaminophen during pregnancy can cause the development of ASD and ADHD in offspring.

The opinions in this report are based upon my education, training, and professional experience, as well as on my review of published literature and other materials cited in this report and in the accompanying Materials Reference List and are expressed to a reasonable degree of medical and scientific certainty or probability.

I will review additional data and information on this matter as they become available.

Wendy K. Chung, M.D., Ph.D.
7/21/2023

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EXHIBIT 2

Materials Considered List

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16. Baccarelli Amended Expert Report Including References and Exhibits

17. Baccarelli Expert Report Including References and Exhibits

18. Baccarelli Redline comparison of Expert Report

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